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Suicide in Twins and Only Children
Franz J. Kallmann, Joseph De Porte, Elizabeth De Porte and Lissy Feingold 113

Heredity of the Rh Blood Types. VIII. Additional Family Studies, with Special Reference to Factor Rh^w
Alexander S. Wiener, Eve B. Gordon and Lillian Handman 127

Blood Types of Brazilian Indians (Matto Grosso)
F. Ottensooser and R. Pasqualin 141

The Incidence of Consanguineous Matings in Japan, with Remarks on the Estimation of Comparative Gene Frequencies and the Expected Rate of Appearance of Induced Recessive Mutations
James V. Neel, Masuo Kodani, Richard Brewer and Ray C. Anderson 156

Turner's Syndrome and Status Bonnevie-Ullrich; A Synthesis of Animal Phenogenetics and Clinical Observations on a Typical Complex of Developmental Anomalies ..... *O. Ullrich* 179

Unilateral Developmental Anomalies in Sisters
C. W. Cotterman and Harold F. Falls 203

Note on the Genetics of Acrokeratosis verruciformis (Hopf)
M. T. Fliegelman and A. B. Loveman 214

Rh Nomenclature ..... *I. B. Wexler* 215

Book Reviews 218

Bibliography of Human Genetics 224

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2

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Suicide in Twins and Only Children[1]

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As an expression of general maladjustment, suicide has long held a focal position among the gloomiest and plainly denotative phenomena of human misery and frustration. Much of the attention attracted by an intentional act of self-destruction stems from the finality of its biological effect and from the palpability of a suicidal behavior pattern, regardless of whether such an act is regarded as a suitable index of cultural inadequacy and social imperfection or as a measure of individual unfitness for survival under frustrating circumstances.

From a genetic point of view, the significance of suicide as a particular form of human behavior is reflected in the rather common tendency to impute the trait to the "fateful" dynamics of organic inheritance in man with practically the same complacent eagerness as has always been true with respect to another outgrowth of civilization associated with generally unpleasant connotations, namely, congenital syphilis. In many theoretical discussions about the relative importance of genetic and environmental factors in human personality development, suicide is likely to be conceded as the least disputable example of a trait determined largely by heredity, while accidental death is often found to be the favorite choice of a condition attributed to strictly environmental influences.

Our first attempt to probe the infinite scope of the human equation of suicide by means of the twin study method was undertaken in 1946 (Kallmann & Anastasio, 1947). The main objective of this investigation was to obtain pertinent information about the usual scheme of causation of self-destructive acts. However, instead of providing some positive evidence concerning common suicidal motivation, the study resulted largely in focussing attention on the motivational complexity of truly intended and successfully executed acts of self-destruction.

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Our analysis was based on the histories of 17 twin suicide cases, six of which had been found in the literature. Despite the limited size of the available material, the statistical result was remarkably plain and distinctly in contrast to popular expectation. Apart from certain exceptional cases of ceremonially disguised or politically dictated forms of simultaneous execution, as well as some rare suicide pacts of two twin partners, it was clearly established by the previous investigation that suicide either was not likely to be committed by both members of a twin pair or, at least, had not been recorded as such in modern times.

Of the original total of 11 discordant twin suicide cases observed in our own series, three occurred in monozygotic, and eight in dizygotic twins. In retrospect, we were unable to find a tangible indication in any of the apparently voluntary cases that the suicidal twin had a clearer motive or a better opportunity to commit suicide than seemed true for the survivor. In fact, in at

TABLE 1. ZYGOCITY AND SEX DISTRIBUTION OF ALL RECORDED TWIN SUICIDES

TWIN SUICIDE CASES	MONOZYGOTIC		DIZYGOTIC		ALL TWIN SUICIDES RECORDED
	Male	Female	Male	Female	
Reported by other investigators	4	*2	—	1	7*
Included in the present study					
With history of psychosis	2	3	5	2	12
Without history of psychosis	2	1	4	5	12
Total umber	8	6	9	8	31

* Including 4 members of 2 possibly concordant pairs.

least three of the dizygotic pairs there was reason to believe that personal achievements and general life conditions had usually been in favor of the suicidal twin. The consistency in discordant behavior with respect to suicide was especially impressive in the monozygotic pairs, since their records revealed pronounced similarities in basic emotional patterns, type of personality, cultural setting, social frustrations, and even in the depressive features of their psychotic histories.

In the meantime, our consecutive series of twin pairs discordant as to suicide has grown in size as well as in observation time. As is tabulated in table 1, the present number of solitary twin suicides, reported to our New York State survey and thus readily available for continuous follow-up observation of the surviving twin partners, has reached a total of 24 sets. An additional discordant case has been placed on record by Vogt and his collaborators (1939). Their collection of monozygotic twins in the higher age groups included a pair of schizophrenic twin sisters, one of whom ended her life by suicide after what was described as "complete recovery" from her psychosis. Since four of the

older cases reported by other investigators were either suicide pacts or questionable in their authenticity, the present total number of twin pairs with suicide of only one member consists of 10 monozygotic and 17 dizygotic sets, an increase of 14 sets. In 23 pairs included in our own survey, the cotwins survived beyond the crucial age period in which the suicides of their twin partners occurred.

The sex distribution of our complete series has reverted to a sex ratio, which is distinguished by an excess of males over females (13 males to 11 females) and now corresponds more closely with statistical expectation. The two groups of twin suicide cases with and without a previous history of psychosis continue to be equally distributed. The proportions of the preferential suicide methods (poisoning, drowning and hanging) have also remained unchanged. The psychiatric classifications of our psychotic twin suicide cases

TABLE 2. DIFFERENTIAL AGE DISTRIBUTION OF SUICIDAL AND SURVIVING TWIN PARTNERS

AGE GROUPS (Years)	MONOZYGOTIC PAIRS		DIZYGOTIC PAIRS	
	Suicidal Twin	Surviving Twin	Suicidal Twin	Surviving Twin
15 to 29	3	1	2	2
30 to 44	1	2	8	1
45 to 59	2	3	—	2
60 to 74	2	1	5	6
75 to 99	—	1	1	4
Average age in years...	44.8	52.6	47.5	62.8
Mean difference in years of survival*...	—	7.9	—	16.9

* Total mean difference: 13.5 years.

include 4 histories of manic-depressive psychosis, 5 histories of involutional, arteriosclerotic and alcoholic psychoses, and 3 histories of schizophrenia.

The differential age distribution of the suicidal and surviving twins of our survey is shown in table 2. The ages at which the suicides occurred ranged from 24 to 69 years in the monozygotic twin cases, and from 26 to 85 years in the dizygotic cases. The average age reached by the suicidal twins was 44.8 years in the monozygotic group, and 47.5 years in the dizygotic group. Accordingly, the total life span which has so far been available to the surviving twins from the time when the cotwins took their lives, amounts to an average of 13 years and 6 months, since the mean difference in survival is close to 8 years in the monozygotic group, and almost 17 years in the dizygotic group. The total range is from 1 to 11 years in the former group, and from 1 to 49 years in the latter group. In spite of these long time intervals which have elapsed by now, and although some of the survivors would seem to have had sufficient

reason to find life just as unbearable as their cotwins did, all of our twin pairs under observation *have remained discordant* as to suicide.

Instead of rendering a lengthy comparative account of the histories of all discordant twin pairs, it may suffice to describe a few typical sets of circumstances under which the partners of monozygotic index cases have survived.

The survivor of the A. twins (fig. 1) is now 73 years old and fully retired, living most of the time at the homes of different relatives. He is more religious than ever and still clearly depressed, but he seems resigned to the loss of his twin brother who drowned himself in 1938. Like the deceased twin, he has been moody, sentimental, and apprehensive. He has a similar history of arrested tuberculosis, hypertensive disease, recurrent depressions, and severe marital maladjustment, and he certainly has ample justification for being dissatisfied with the degree of his economic security and professional achievements. His pliant state of humility is well characterized by a quotation from a recent letter in which he described his lonesome life as follows:

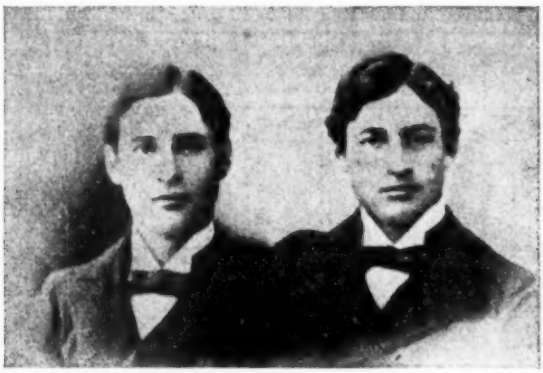

FIG. 1. The A. Twins at age 22 yr.

"My happiest experience is the morning hour from 6 to 7, which I spend reading the Bible and praying, and my growing conviction is that the person who most dares to expose his soul daily to the Word of God is he who will most determine the intellectual, moral and spiritual trends of generations to come."

The interim developments in the history of Mary, the surviving member of the N. twins (fig. 2), were distinguished by even greater traumatic potentiality. The original similarities included a very poor home background, severe acne, and a catatonic type of schizophrenic psychosis which responded well to insulin treatment. Following Nelly's suicide in February 1944 and the sudden death of the mother a few months later, Mary kept house for her father until he remarried and abruptly withdrew his support from her. She left his home when, according to her own report, "he hurt her very much by coming out with the statement that he expected her to commit suicide like Nelly did." She continued to feel very guilty about her twin sister's death, went through an unhappy love affair with her employer, and lost her job as a waitress when her acne condition recurred. She spent all her savings for dermatological treatment and the support of a brutal and shiftless suitor, whom she married against advice and her own better judgment after she had become pregnant. Although the

child died at birth and her husband deserted her several times, she made every possible effort to live with him and keep him out of trouble. Last year she followed him to the West Coast where she was stranded without support for several months. According to most recent reports, her experiences have continued to be a notable record of the extent to which human life is adaptable to adverse circumstances.

FIG. 2. The N. Twins at age 2 yr.

FIG. 3. The R. Twins at age 9 yr.

The histories of a third pair of monozygotic twins (fig. 3) may serve to show that the apparent irrationality and explosive impulsiveness of certain suicidal acts may reach a point where suicide would seem to have been committed by the wrong twin. The R. twins grew up together in a small upstate community and for many years appeared inseparable as well as indistinguishable, sharing the questionable reputation of boisterous, violent and completely unrestrained philanderers who indulged heavily in alcohol.

Following his marriage into a stable and substantial family at the age of 30, Richard discontinued his excessive drinking, became a successful businessman, and strictly adhered

to the life of a popular and highly respected member of his community. He enjoyed apparently good health, worked hard, seemed jovial and fully contented, and never showed any signs of uneasiness or depression. When he committed clearly intentional suicide at the age of 54, the motivation of his act was inexplicable to every one, since his family life was happy, his business prosperous, and his social status appeared free of any personal problem.

The twin brother remained single, never reformed and continued to decline socially along the pattern of a shiftless and irresponsible alcoholic. He left his home town after Richard's death, and since that time has failed even more plainly to free himself from the repercussions of his frustrated existence. However, it may have been this very lack of self-restraint in availing himself of the potentialities of illusive escape provided by alcohol, which somehow enabled him to survive his twin brother, whose social position and family responsibilities apparently prevented him from the use of equally unrestrained outlets.

By contrast, the life records of the W. twins, Willard and William, another monozygotic pair (fig. 4), matched in all essential aspects till senescence, except for a slight limp which Willard retained from a childhood accident. The twins were brought up on their father's

FIG. 4. The W. Twins at age 18 yr.

prospering farm, attended the same schools, were equally popular, and went into business together. They held similar positions with the same degree of discretion and efficiency and were active in church work and community affairs, although inclined to be tense and somewhat morose in their outlook on life. Remaining closely attached to one another despite numerous personal arguments, they continued to live under the same roof even after their equally conventional marriages, which were childless but apparently harmonious.

Following an uncomplicated goiter operation at the age of 50, William distrusted his ability to regain sufficient physical strength and began to show symptoms of moodiness, listlessness and discontentment. He worked less regularly than Willard, antagonized many people around him by increasing querulousness, and frequently talked of the desirability of suicide. Nevertheless, he surprised everybody when he ended his life by shooting himself through the head, three days before his seventieth birthday.

A few months later, Willard's wife developed a severe cardiovascular disorder, which soon led to her death and further aggravated his own state of despondency and loneliness. He has remained dejected and disconsolate ever since, bemoaning his cheerless and misanthropic life and talking of suicide upon the slightest provocation. However, he is 82 years old at the present time and still works during the season and around the house

The *general significance* of the observation, that monozygotic twin partners seem entirely disinclined to establish concordance as to suicide, is evident biologically as well as psychologically. It is also clear, however, that the apparently consistent disinclination of twins to behave concordantly in relation to suicide is open to completely different interpretations.

One hypothetical explanation would be that concordance as to suicide does not occur in twins, because the surviving partner may be *immunized* psychologically against yielding to any self-destructive trends. It may be postulated, for instance, that self-destruction as a possible solution is no longer available to the survivor on account of painful and deterrent memories of the closely observed circumstances incidental to a suicide or because of the survivor's tendency to identify himself so completely with his suicidal cotwin that he is not able any more to feel or to act like a living person. In other words—but without a change in the semantic context of this hypothetical allegory—the basic implication of a shocking and overpowering identification mechanism would be that it prevents an already deceased individual from "taking his life a second time."

Another psychological explanation might be based on the popular psychodynamic theory that a suicidal act results from a regressive state of dejection and introjective aggressiveness following the presumably irrecoverable loss of a love object and consequent ambivalence toward it. The psychological inference would be that no one commits suicide who is not obsessed by the urge of punishing another person to the extent of wanting to annihilate himself instead of the hated object. If applied to the strong attachment formed by twin partners, this concept would imply that persistence and ambivalent intensification of sibling rivalry in adult life create the most powerful motive for self-destruction in the first members of sibship pairs who cannot detach themselves from an especially competitive situation. It would follow, then, that the suicide of the first twin partner is bound to lead to such a dramatic relief of a chronic state of tension that the survivor would find himself deprived not only of a suitable object for further competition and projection, but also of a sufficiently strong motive for his own suicide at a later date.

Neither explanation impressed us as satisfactory in our previous analysis. At that time, however, only one of them, namely, the hypothesis based on the phenomenon of identification, could be rejected with any degree of certainty. According to this hypothesis, one should expect that all the surviving twin partners tend to identify themselves with their deceased cotwin and, therefore, would be protected from suicide even if the death of the partner had been due to causes other than suicide. However, there is no evidence to substantiate this presupposition, nor is there any reason to question the ability of twins to readjust their lives to the ordinary conditions of single-born persons following the loss of their partners. In fact, our survey includes several pairs in whom one member committed suicide after his cotwin had died of natural causes,

and we know of even more instances in which surviving twins made a very satisfactory adjustment to the realities of a solitary life.

The inadequacy of the other explanation was much more difficult to demonstrate. Its emphasis was on the factor of intensified sibling rivalry as the principal cause of one twin partner's self-destruction, and on the cotwin's immunity to suicide following elimination of the ambivalent sibling relationship. The obvious corollary of this hypothesis would be, however, that "only children" can be shown to have a significantly lower suicide rate than is found in persons of the same age group, who had at least one sibling while they were alive. Unless complete lack of a sibling materially reduces the chance of self-destructive acts, neither the persistence of sibling rivalry nor the possession of a thoroughly hated relative can be regarded as sufficient to explain the commitment of homicide or suicide.

When our previous investigation had reached this crucial point, we were first inclined to take the common occurrence of suicide in only children more or less for granted. However, as soon as we attempted to substantiate our presumption by means of some available histories, the technical and statistical difficulties of the problem became immediately apparent. We neither succeeded in verifying more than a few isolated cases of suicide in persons who had definitely no siblings nor were we able to obtain adequate information about the general expectancy rate of such cases. We decided, therefore, to keep the entire question of suicide in only children in abeyance in order to gain time for the procurement of reliable data from a statistically representative sample.

In collaboration with the Office of Vital Statistics of the New York State Department of Health, this additional investigation has meanwhile been completed. The data collected appear interesting enough to warrant recording for the purpose of similar comparative studies.

Since the principal statistical aim of this analysis was to determine whether suicides are more or less common among only children than among persons with brothers or sisters, we investigated the death and birth certificates of an unselected sample of 492 suicides certified in the State (outside of New York City) between January 1944 and May 1946. In view of the fact that the registration of births with the State Department of Health became effective only in 1880, the analysis was limited to residents of the State, who were born in upstate New York and were under 65 years of age at the time of death. This procedure reduced the available number of suicides with corresponding birth and death certificates to 296 recorded cases, that is, to 60.2 per cent of the entire sample.

In 243 of the 296 index cases examined for the number of children ever born to their mothers, it was possible to establish immediately that the suicidal members of the given sibships had not been only children, because there

had been previous siblings. The possibility, that some siblings born previously might have died prior to the birth of the index cases, appeared negligible for the purposes of this investigation. Even forty or fifty years ago, infant mortality did not exceed a rate of one per cent, and many of the births were to mothers who had already had several children.

The group of possible only children among the index cases was now diminished to 53 suicidal persons (17.9 per cent), who had been the first children born to their mothers. A further reduction to 39 index cases took place when a search was made for subsequent siblings born during a three-year period following each birth. The histories of the remaining group of 39 index cases who still were possible only children were investigated through personal visits to surviving members of the given families.

In this manner it was definitely established that 12 suicidal index cases had been only children, while additional siblings were found in 7 cases. No adequate information was obtained with respect to the remaining group of 20 suicides, since we could not locate a person familiar with the histories of the given

TABLE 3. WHITE WOMEN 45–74 YEARS OF AGE BY NUMBER OF CHILDREN EVER BORN; NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY, 1940

	45–49 YEARS	50–74 YEARS
Total women	130,320	393,920
Number with one child only	28,220	87,580
Total children born to these women	433,020	1,357,480
Per cent of only children	6.5	6.5

families. However, it can be stated with certainty that our sample of 296 suicides included at least 12 persons, or 4.1 per cent, who were only children, while the maximum possible number would have been 32 cases, or 10.8 per cent.

The aim of the next step of the analysis was to determine the expected number of only children to be found in a sample of 296 deaths. Unfortunately, no statistical data were available regarding the number of only children in the general population according to age. However, the fertility tables of the 1940 census (*Cf. References*) provided some tabulations according to the number of children ever born to mothers of various ages. From these tables it was possible to compute the percentage which only children formed of all children born to mothers surviving at these ages. This figure is 6.5 per cent, if the computation is limited to white mothers between the ages of 45 and 75, who were living in upstate New York (table 3).

The standard deviation of 6.5 per cent in a sample of 296 cases is 1.4 per cent. In other words, if the rate of only children were the same among persons who committed suicide as it may be assumed to be among the members

of the general population (as represented by the children of mothers for whom comparable data were obtained at the 1940 census), the percentage in successive samples of 296 cases would vary between 6.5 minus 2.8, or 3.7, and 6.5 plus 2.8, or 9.3. Since the minimum rate of only children in our sample has been found to be 4.1 per cent, this rate is clearly *above* the expected minimum. The maximum rate, which at 10.8 per cent must be regarded as obviously too high, exceeds the expected maximum only by a negligible margin.

As a control, another approach can be used in order to determine whether the number of first children among suicidal index cases is higher or lower than is to be expected. The supposition is that if the proportion of only children

TABLE 4. COMPARISON OF THE PROPORTION OF FIRST CHILDREN IN SUICIDE DEATHS AND DEATHS FROM OTHER CAUSES

AGE AT DEATH (Years)	DEATHS FROM SUICIDE			DEATHS FROM OTHER CAUSES		
	Total	First Children		Total	First Children	
	No. n_1	No. d_1	Per cent p_1	No. n_2	No. d_2	Per cent p_2
15 to 19	21	4	19.0	12	2	16.7
20 to 24	20	6	30.0	28	6	21.4
25 to 34	58	11	19.0	26	5	19.2
35 to 44	82	13	15.9	49	10	20.4
45 to 54	81	11	13.6	65	5	7.7
55 to 64	34	8	23.5	80	17	21.3
All ages.....	296	53	17.9	260	45	17.3

Analysis of differences (p_1-p_2) in proportion of first children among suicidal deaths and other deaths:

	χ^2	D.F.	P
Sum of χ^2's for 6 separate age-at-death groups.....	2.280	6	
Over-all difference (all age groups combined).....	0.034	1	>0.80
Heterogeneity of p_1-p_2 difference.....	2.246	5	>0.70

among suicides were significantly reduced, the proportions of first births among them should be correspondingly low.

With respect to this procedure, more comprehensive comparative data were available, namely, the birth certificates for persons who died from causes other than suicide (table 4). The sample of control cases used in the analysis consisted of 426 death certificates recorded in June 1946. These cases were investigated in the same manner as had been the suicide records. After corresponding birth certificates had been found for 260 index cases (61.0 per cent of the total), it was established that 45 of them, or 17.3 per cent, had been first children. The corresponding proportion for suicidal index cases was 17.9 per cent.

In order to test the significance of the difference between the proportions

of first children in the two samples, it was necessary to take variations in age at death into account. Since suicidal persons as a group tend to be younger than are those dying from other causes, the decline in the birth rate made it inevitable that the number of children ever born to a mother depended partly on the year in which an index case was born. If this factor is taken fully into consideration (table 4), there appears to be *no significant difference* between the proportions of first children included in the two samples.

On the basis of these findings it finally is justified to conclude that the number of only children among persons with self-destructive tendencies does not differ significantly from the expected number as deduced from data available with respect to the general population. Evidently, only children are neither more likely nor less likely to commit suicide than are any other persons, including those who had an opportunity to perpetrate sibling rivalry or to develop identification mechanisms in intimate sibship relations.

In view of the impossibility of interpreting the observation of suicidal discordance in twin pairs on strictly psychological grounds, we must search for other explanations. Such explanatory factors may be either statistical in nature or related to the methodology of suicide.

It may be suggested by some one not quite familiar with the extent of the modern literature on twins, that suicidal concordance of monozygotic twin partners has not been observed because it has not been recorded with sufficient regularity, especially when the twin suicides occurred at different times and widely different places. However, it never seemed probable that concordant behavior of twin partners with respect to suicide should not have been of sufficient interest to some observer to instigate publication or a direct note to our survey, and this improbability has practically become an impossibility since the time when our first report on twin suicides appeared. As far as we know, there are no other concordant twin observations including accidental death at different times, which have not been recorded, nor is there any reason to believe that the suicides of twin partners would arouse less interest than is true of simultaneous deliveries or tonsillectomies of twins. In any case, we have not received either a personal communication or any other piece of information that would require a revision of our previous statement that suicide does not seem to occur in both members of a twin pair.

It would be equally inappropriate to explain this apparent discordance as to suicide on the basis of a generally reduced prevalence of self-destructive acts in persons who are twins. The previously recorded sample of 296 suicides includes 4 individual members of twin pairs with a surviving partner. This proportion is in complete correspondence with statistical expectation.

The only remaining explanation of sufficient plausibility is that the suicides of two twin partners are possible psychologically and thus are apt to occur, but that they are not directly related to one another even under similar condi-

tions of unfavorable family background, social frustration, or emotional maladjustment. If this theory is correct, concordance as to suicide will only be observed *by chance* and, therefore, will be *extremely rare*. Since neither twinning nor suicide tends to be especially common as such, and since some instances of suicide may not be recognized or recorded, the random observation of a similar cause of death in the cotwin of a suicidal index case is to be expected to be very uncommon within the limits of any available sample and a specified period of time. The number of twins born in the United States approximates 2 per cent of all births, while suicides constitute a little more than 1 per cent of the total death rate. The annual number of deaths in the total population was 1,385,187 in 1942 and included 16,117 recorded suicides.

More precisely, the probability that a male child born in the United States will eventually commit suicide is 1 in 50 under present conditions (Dublin & Bunzel, 1933; Dublin & Lotka, 1936). Births of male twins number approximately 15,000 a year. About 300 of them ($15{,}000 \times 1/50$) would be expected, therefore, to end their lives by self-destruction, if one assumes that twins survive childhood at the same rate as single-born children, that is, if one disregards a moderate increase in the infant mortality rate of twins. Provided that the chance of committing suicide is neither increased nor decreased for the partners of suicidal twins, the maximum random expectancy for this group of cotwins would be a total of 6 suicides ($300 \times 1/50$). In other words, the number of male twin pairs born in the United States, both members of which may be expected to be candidates for suicide at some time during their lifetime, should not exceed an average of 6 sets a year.

Some of these suicides will be committed at widely different times and locations, while others may occur under particularly obscure circumstances. Since the certifiable observation of these cases is not likely to fall within the limits of a state-wide survey such as the present, it seems justified to conclude that random concordance of twin pairs as to suicide, although not precluded by special biological or psychological laws, will be so rare in any given sample that discordance should be the expected rule.

In any case, the established disinclination of the suicide rate to show any increase in concordance in a consecutive series of monozygotic twin pairs, even in those distinguished by pronounced similarities in social frustrations and psychopathological phenomena, may be regarded as sufficient to refute the possibility of a special genetic factor predisposing a person to the commitment of self-destruction. This refutation does not preclude the potential significance of family tradition, cultural custom or unusual social deprivation in playing a part in the concurrence of several suicides in a few selected family units. However, it evidently conflicts with the popular theory that the tendency to commit suicide runs in families as a hereditary trait.

This theory has been based on generalized impressions or isolated casuistic

reports rather than on adequate statistical data, and it certainly disregards the possibility that a limited accumulation of suicides in some families may have been due to chance. For instance, it should be remembered in view of the figures quoted above that the probability of any two brothers committing suicide is $(\frac{1}{80})^2$. Since there are about 1,250,000 male births a year in the United States, as many as 500 cases a year should be expected in which a man committing suicide has a brother who died in a similar manner. It is in accordance with expectation, therefore, that occasional instances of a familial accumulation of suicides are observed and recorded.

The implications of this statement make it possible to formulate a number of *generally valid conclusions* regarding the causation of suicide:

(1). Biologically as well as psychologically it seems inadequate to apply simple analogies, inferred from the observation of ineffective suicide attempts, to the motivational dynamics of successfully executed acts of self-destruction. Some threats of suicide may actually be completed because they somehow succeed by accident, and a few truly intended acts may be thwarted by an unusual constellation of circumstances beyond the control of the dejected person. In the majority of suicidal cases, however, there is a distinct and apparently qualitative difference between the psychobiological mechanics of attempted and fully accomplished suicides. Effective self-destruction requires the sudden and complete suppression of the vital controls of self-preservation, while the human capacity for adaptation to stress and competition predominates in abortive acts.

(2). As a rule, therefore, successful suicides cannot simply be explained by a certain type of personality and genetic constitution, or by a particular combination of social frustration and personal distress, or by the effect of a special psychotic syndrome. Each of these factors may be capable of playing an essential part in the causation of certain acts of suicide. However, they cannot be expected to lead invariably to a final choice of suicide even if all of these factors happen to coincide in a potential candidate for self-destruction. The main exception concerns essentially involuntary acts of self-destruction enforced by religious custom, political compulsion, or other severe threats of an apparently irresistible force. According to a preferential system of classification offered by Nolan D. C. Lewis (1933–34), most of these cases should be regarded as ceremonial or politically enforced forms of capital punishment.

(3). The main psychiatric inference to be drawn from a study of suicide in an unselected series of twin pairs may be seen in the conclusion that completed suicidal acts on a progressive cultural level seem best defined as a compulsive and certainly abnormal type of short-circuit reaction of a person in distress. The psychopathology of this reaction may be described as an unusual "*twilight state of self-destructive ecstasy*" in response to the inability to adjust to the pressure of adverse life conditions. The release of a truly intended self-de-

structive action is the outcome of such a peculiar combination of motivational factors as to render a duplication of this complex high-tension state very unlikely even in identical twins who show the same type of mental disorder and a very similar degree of social privation.

(4). The high-tension state required for the release of a suicidal trigger mechanism is uniform only as to the finality of its biological effect, but not in the composition of the various motivational factors which may be involved. It is safe to assume, however, that a gradual accumulation of tension is necessary for the final release of this trigger mechanism even in those suicides which appear carefully prepared.

(5). There is no statistical evidence for the popular notion that the tendency to commit suicide recurs in certain families as the result of a special hereditary trait or of a particular type of genetically determined personality deviation. The observation of occasional instances of a familial accumulation of suicides seems as much in accordance with statistical expectation as is the relative rareness of the random finding of suicides committed by two members of a twin pair, either monozygotic or dizygotic.

(6). There is no reason to believe that the emotional tension state giving rise to the activation of an effective suicidal impulse is influenced materially by such particular psychological mechanisms as intensified sibling rivalry or special identification phenomena occurring in twins. Of particular interest is the observation that the suicide rate of only children does not differ significantly from that of the general population or from that of twins. The conclusion to be drawn from this finding is that neither the overprotected position of only children nor the intensified competition between twins appears to result in an increased vulnerability to suicidal impulses.

REFERENCES

DUBLIN, L. I., & BUNZEL, B. 1933. *To Be or Not To Be; A study of suicide.* New York: Harrison Smith & Robert Haas, pp. 443.

DUBLIN, L. I., & LOTKA, A. J. 1936. *Length of Life.* New York: Ronald Press Co., pp. 400.

KALLMANN, F. J., & ANASTASIO, M. M. 1947. Twin studies on the psychopathology of suicide. *J. Nerv. Ment. Dis.* 105: 40–55.

LEWIS, N. D. C. 1933–34. Studies on suicide. *Psychoanal. Rev.* 20: 241–273, and 21: 146–153.

U. S. BUREAU OF THE CENSUS. *Sixteenth Census of the United States. 1940 Population:* Differential Fertility 1940 and 1910. Fertility for States and Large Cities. pp. 111-222.

VOGT, A., WAGNER, H., RICHNER, H., & MEYER, G. 1939. Das Senium bei eineiigen und zweieiigen Zwillingen. *Arch. Julius Klaus Stift.* 14: 475–595.

Heredity of the Rh Blood Types

viii. Additional Family Studies, with Special Reference to Factor rh^w

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THIS paper represents a continuation of studies on the heredity of Rh types. In previous papers of this series observations were reported on a total of 723 families with 1249 children; in this report an additional 200 families will be described. In each succeeding paper of the series, the complexity of the investigations has increased as more and more Rh and Hr antisera became available for use in our routine work and in the family studies. In the present study, all bloods have been tested with sera of specificities, anti-Rh_0, anti-rh′, anti-rh″, and anti-hr′; most were tested with anti-hr″ serum, while 46 of the families were also tested with anti-rh^w serum.

MATERIALS AND METHODS

As in previous studies, the families tested represent principally clinical cases which had been referred for antenatal Rh-Hr tests and for Rh antibody titrations, or which were studied because the mother had given birth to a baby with jaundice and anemia, or had an obstetrical history of stillbirths or neonatal deaths suggestive of erythroblastosis. This accounts for the marked excess of types rh, rh′, rh″, and rh′rh″ among the mothers in the family material presented. The Rh-Hr tests were carried out in the usual way by the tube agglutination method, while the A-B-O and M-N tests were carried out on a well-slides as described in previous papers. The authors are indebted to Dr. B. Broman for the anti-rh^w serum which was used for testing the last 46 families of the present series.

NOMENCLATURE

Since the previous papers were written, there has been considerable increase in knowledge and understanding of the serology and genetics of the Rh-Hr types, particularly in regard to the so-called "intermediate" Rh factors (Wiener, 1944; Unger & Wiener, 1949) and the factor rh^w or C^w of British investigators (Callender & Race, 1946; Race *et al.*, 1948; Wiener & Gordon, 1949; Wiener, Unger & Mazzarino, 1949). In view of the newer findings, there is no further reason for using duplicate systems of notations for the Rh-Hr types. Thus, there now exists an international nomenclature (Wiener 1949*b*) for the Rh-Hr types just as there is for the A-B-O groups and M-N types.

For convenience of reference, there is presented in table 1 a summary of the evolution of the knowledge of the Rh-Hr types as more and more Rh and Hr

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antisera were discovered. The serum, anti-Hr_0, which was the last to be found,[15] is of considerable practical importance but unfortunately is still not available except in the laboratories of the discoverers. Table 1 does not include the rh^w factor or the "intermediate" Rh factors, which have been deliberately omitted in order not to complicate the picture too greatly.

In the present state of knowledge, the following nine Rh genes have been completely identified: r, r', r'', r^y, R^0, R^1, R^2, R^z, and R^{1w}. Taking only the first eight genes into consideration, as many as 36 different genotypes are theoretically possible, which are listed in the last column of table 1. These 36 genotypes differ widely in their incidence in a population, due to the considerable differences in the gene frequencies. Thus, some of the genotypes are so rare that for practical purposes they may be disregarded. The rarest genotype is r^yr^y, which theoretically occurs only once among every 100,000,000 Caucasians. Moreover, the actual serological tests do not identify genotypes but phenotypes, and the number of phenotypes which can be distinguished depends upon the number of antisera used in the actual serological tests. Thus, when only the original anti-Rh_0 serum (or "standard" Rh serum) is used only two phenotypes are distinguishable, while antisera rh′ and rh″ increase the number of phenotypes to eight. Further, when hr′ and hr″ antisera are used, the number of distinguishable phenotypes is increased to 18, while the addition of anti-Hr_0 serum increases the number of phenotypes to 27. Thus, there is not a one-to-one correspondence between phenotypes and genotypes, and to make a precise genotype diagnosis on the basis of the serological tests alone is bound to lead to serious mistakes. In the International Nomenclature of the Rh-Hr types, therefore, distinctive designations are employed to differentiate phenotypes from genotypes, and it is possible to tell from the phenotype name exactly which of the antisera were actually used in the tests and what reactions were obtained.

In a few cases it is possible to infer the exact genotype from the phenotype. For example, under the theory of multiple alleles, all bloods of phenotype rh belong to genotype rr, all bloods of phenotype rh′rh belong to genotype $r'r$, etc. (see table 1). In most cases, it is necessary to supplement the serological test on the individual with additional tests on his family in order to diagnose the exact genotype. And in some cases, even this supplementary information is not adequate to permit an exact diagnosis of genotype. For example, it is important from a clinical standpoint to bear in mind that type Rh_1rh individuals are not always heterozygous for the Rh_0 factor. This is especially important when forecasting the outcome of future pregnancies of sensitized type rh women with type Rh_1rh husbands. If one of the husband's parents or if any of his children belong to type rh, this is proof that he is heterozygous (genotype R^1r). On the other hand, if such a man has one or more children of type Rh_0 and others of type Rh_1 then his genotype must be R^1R^0, and for clinical purposes he should

TABLE 1. THE RH-HR PHENOTYPES AND GENOTYPES (AFTER WIENER, A. S. 1949. *Bull. Dade Co. M. Ass.* 20: 20-32)

TABLE 1. THE RH-HR PHENOTYPES AND GENOTYPES (AFTER WIENER, A. S. 1949. *Bull. Dade Co. M. Ass.* 20: 20–32)

2 Rh phenotypes			8 Rh phenotypes				18 Rh-Hr phenotypes				27 Rh-Hr phenotypes			
Desig-nations	Approximate frequencies in N.Y.C. whites (%)	Reaction with anti-Rh_0 (or anti-rhesus)	Desig-nations†	Approximate frequencies‡ in N.Y.C. whites (%)	Reaction with Anti-rh'	Reaction with Anti-rh''	Desig-nations	Approximate frequencies‡ in N.Y.C. whites (%)	Reaction with Anti-hr'	Reaction with Anti-hr''	Desig-nations	Calculated frequencies in N.Y.C. whites (%)	Reaction with Anti-Hr_0	Genotypes
Rh negative	14.9	–	rh	13.4	–	–	rh	13.4	*	*	rr	13.4	*	rr
			rh'	1.1	+	–	$rh'rh'$	.02	–	*	$r'r'$	.02	*	$r'r''$
							$rh'rh$	1.1	+	*	$r'r$	1.1	*	$r'r$
			rh''	0.4	–	+	$rh''rh''$	.003	*	–	$r''r''$	.003	*	$r''r'''$
							$rh''rh$	0.4	*	+	$r''r$	0.4	*	$r''r$
			$rh'rh''$ (rh_y)	.02	+	+	rh_yrh	.02	+	+	r^yr	.02	*	r^yr and $r'r'''$
							rh_yrh'	.0003	–	+	r^yr'	.0003	*	r^yr'
							rh_yrh''	.0001	+	–	r^yr''	.0001	*	r^yr''
							rh_yrh_y	.000001	–	–	r^yr^y	.000001	*	r^yr^y
Rh positive	85.1	+	Rh_0	2.5	–	–	Rh_0	2.5	*	*	R_0R_0	0.1	–	R^0R^0
											R_0r	2.4	+	R^0r
			Rh_1	51.2	+	–	Rh_1Rh_1	16.0	–	*	R_1R_1	16.9	–	R^1R^1
											R_1r''	1.1	+	R^1r''
							Rh_1rh	33.2	+	*	R_1R_0	2.6	–	R^1R^0
											R_1r	30.6	+	R^1r and R^0r'
			Rh_2	16.5	–	+	Rh_2Rh_2	2.9	*	–	R_2R_2	2.7	–	R^2R^2
											R_2r''	0.2	+	R^2r''
							Rh_2rh_1	13.6	*	+	R_2R_0	1.1	–	R^2R^0
											R_2r	12.5	+	R^2r and R^0r''
			Rh_1Rh_2 (Rh_z)	14.9	+	+	Rh_2Rh_0	14.8	+	+	R_2R_0	13.9	–	R^2R^0 and R^1R^2
											R_2r	0.9	+	R^2r, R^1r''', R^0r, R^0r^y
							Rh_2Rh_1	.09	–	+	R_2R_1	.08	–	R^2R^1
											R_2r'	.001	+	R^2r' and R^1r^y
							Rh_2Rh_2	.03	+	–	R_2R_2	.03	–	R^2R^2
											R_2r''	.0004	+	R^2r'' and R^0r^y
							Rh_2Rh_2	.0001	–	–	R_2R_2	.0001	–	R^2R^2
											R_2r^y	.00002	+	R^2r^y

* The asterisks in the table indicate tests which need not be made since they are invariably positive.

† In this table Rh_1 is used as a short designation for Rh_0'; Rh_2 is short for Rh_0''; rh_y is short for rh''', and Rh_z is short for Rh_0'''.

‡ Based on more than 1000 tests.

TABLE 2. LIST OF FAMILY MATERIAL

FAMILY NO.	FATHER	MOTHER	CHILDREN		
1	A_1MRh_1rh	OMrh	A_1Mrh ♀		
2	$A_1MNRh_1Rh_1$	OMrh	$OMRh_1rh$ ♂	A_1MNRh_1rh ♀	
3	$A_1MRh_1Rh_1$	OMNrh	$OMRh_1rh$ ♀ $OMRh_1rh$ ♀	A_1MRh_1rh ♀	$OMRh_1rh$ ♀
4	$OMNRh_0$	A_1MNrh	$AMNRh_0$		
5	$OMNRh_1Rh_1$	OMrh	$OMNRh_1rh$		
6	$BMRh_2Rh_0$	$OMRh_2Rh_0$	$BMRh_2Rh_0$ ♂		
7	$BMNRh_2Rh_0$	A_1MNrh	A_1MNRh_2rh ♀	ABMrh′rh	
8	$A_1MNRh_1Rh_1$	ONrh	A_1MNRh_1rh ♀	$A_1MNrh'rh$ ♂	$ONRh_1rh$ ♀
9	A_1MNRh_1rh	$A_2MRh_1Rh_1$	$A_1MNRh_1Rh_1$ ♂		
10	A_1NRh_1rh	A_1Mrh	A_1MNrh ♂	OMNrh ♀	
11	$OMNRh_1Rh_1$	OMNrh	$OMRh_1rh$ ♂	$OMRh_1rh$ ♀	$OMNRh_1rh$ ♀
12	A_2MNRh_1rh	A_1Mrh	OMrh ♂		
13	A_1Mrh	BMrh	A_1BMrh ♀		
14‡	$OMNRh_1rh$	BNrh	ONrh ♂	$BMNRh_2rh$ ♀	
15	$OMNRh_1rh$	A_1MNrh	$OMRh_1rh$ ♂		
16	A_1BMRh_1rh	$OMRh_1Rh_1$	$BMRh_1Rh_1$		
17	A_1BMNRh_1rh	BMNrh	BMNrh ♂	BMNrh ♀	
18	$A_1MNRh_2Rh_0$	$OMNRh_1rh$	$A_1MNRh_1Rh_1$ ♂	$AMRh_1rh$ ♂	
19	$A_1MNRh_2Rh_2$	A_1MNrh	A_1MNRh_2rh ♀	A_1NRh_2rh ♂	
20	$ONRh_2Rh_0$	BMrh	$OMNRh_2rh$ ♂	$OMNRh_2rh$	
21	$OMRh_1rh$	ONrh	OMNrh ♂	OMNrh ♂	
22	$A_1MNRh_1Rh_1$	A_2Nrh	$ONRh_1rh$ ♂		
23	$A_2MNRh_2Rh_0$	$OMNRh_2Rh_0$	$OMRh_2Rh_0$ ♂	$A_2MRh_1Rh_1$ ♂	
24	$OMNRh_1Rh_1$	BMNrh	$BMNRh_1rh$ ♀	$BMNRh_1rh$ ♂	$OMNRh_1rh$ ♀
25	$BMRh_2rh$	OMrh	OMrh ♂	$OMRh_2rh$ ♀	
26	$A_1MNRh_1Rh_2$	$A_1NRh_1Rh_2$	A_2NRh_2 ♂		
27	$OMNRh_1Rh_1$	$BMNRh_1rh$	$ONRh_1rh$ ♂		
28	$OMNRh_2rh$	A_1MNrh	A_1MNrh ♂		
29	$A_1BMNRh_1Rh_1$	A_1MNrh''	A_1BMNRh_1rh ♀		
30	$BMRh_2$	A_1MNrh	A_1BMNrh ♀	A_1BMRh_2 ♀	
31	$OMRh_1rh$	A_1MNrh	A_1MRh_1rh ♀	AMrh	
32	A_1MNRh_1rh	$OMNRh_1rh$	A_1NRh_1rh ♀		
33	$ONRh_1rh$	A_1MNrh	$OMNRh_1rh$ ♂		
34	$OMRh_1rh$	A_2Nrh	A_2MNrh ♀	$OMNRh_1rh$ ♀	
35	$OMNRh_2Rh_1$	ONrh	$OMNRh_2Rh_0$ ♂	$OMNRh_2Rh_0$ ♂	
36	$A_1MNRh_1Rh_1$	A_1MNRh_1rh	A_1MNRh_1rh ♀		
37	$OMNRh_1rh$	$OMRh_1Rh_1$	$OMNRh_1Rh_1$		
38	OMrh	$OMRh_2rh$	$OMRh_2$ ♀		
39	$OMNRh_2Rh_0$	$OMNRh_1Rh_1$	$ONRh_1Rh_1$ ♂		
40	A_1MNRh_1rh	ONrh	$OMNRh_1rh$ ♀	A_1MNRh_1rh ♀	
41	$BMNRh_1Rh_1$	A_1Nrh	A_1MNRh_1rh ♀	A_1BMNRh_1rh ♂	
42*	$ONRh_2rh$	OMNrh′rh	ONrh′rh ♂	OMNrh′rh ♂	OMNrh′rh ♂
43	$BMNRh_2Rh_0$	A_1MNRh_1rh	$A_1MNRh_2Rh_0$ ♀		
44	$OMNRh_1rh$	A_2Nrh	OMNrh ♀	A_2MNRh_1rh	
45	$A_1MNRh_1Rh_1$	$OMNRh_1rh$	A_1Rh_1rh	$A_1MRh_1Rh_1$ ♂	
46	$OMNRh_1rh$	A_2Mrh	A_2MRh_1rh ♀	$OMRh_1rh$ ♀	

TABLE 2.—*Continued*

FAMILY NO.	FATHER	MOTHER	CHILDREN		
47	$OMNRh_1rh$	OMrh	$OMNRh_1rh$ ♂	OMNrh ♀	
48	$A_1MNRh_1Rh_1$	OMNrh	$OMRh_1rh$ ♀		
49	$OMNRh_2rh$	BMrh	$OMNRh_2rh$ ♀		
50	$OMNRh_1Rh_1$	BNrh	$BNRh_1rh$ ♀		
51	$BMNRh_1Rh_1$	A_1MNrh	$ONRh_1rh$ ♂	$BMNRh_1rh$ ♂	
52	A_1Nrh	BMNrh	BNrh ♂		
53	$A_2BNRh_1Rh_2$	OMNrh	A_2MNRh_2 ♀		
54	$OMNRh_1rh$	A_2Nrh	$OMNRh_0$ ♂	$ONRh_1rh$	
55	A_1BMNRh_1rh	A_1BMNrh	A_1BMNRh_1rh♂	A_1Mrh ♀	$ABNRh_1rh$
56	ONrh	$BNRh_1Rh_1$	$ONRh_1rh$ ♂		
57	A_1NRh_2rh	A_1Nrh	A_1Nrh ♀	$ONRh_2$ ♀	ANrh ♂
58	$OMNRh_1rh$	A_1Mrh	$A_{1\cdot2}MRh_1rh$ ♀	A_2MRh_1rh ♂	A_2MNrh ♂
59	$OMNRh_1Rh_1$	ONrh′rh	$OMNRh_1Rh_1$ ♂	$OMNRh_1rh$ ♀	
60	A_2NRh_0	BMNrh	$BMNRh_0$ ♂		
61	$A_1MNRh_1Rh_1$	OMNrh	A_1MNRh_1rh ♀		
62	$OMRh_1Rh_1$	ONrh	$OMNRh_1rh$ ♂	$OMNRh_1rh$ ♂	
63	$OMRh_1Rh_1$	A_1MNrh	$OMNRh_1rh$ ♂		
64	$A_1BMRh_2Rh_1$	OMrh	A_1MRh_1rh ♂	$A_1MRh_2Rh_0$ ♂	
65	A_1MNRh_2	$A_1BMNrh′rh″$	$A_1MRh_1Rh_2$ ♀	A_1MRh_2 ♀	
66	BMrh	A_1BMNRh_2	$BMRh_2$ ♀		
67	A_1MNRh_1rh	$OMNRh_2Rh_0$	$A_1MNRh_1Rh_1$ ♀	$OMNRh_1rh$ ♀	
68	A_1MRh_1rh	A_1Mrh	A_1Mrh ♀		
69	$A_1NRh_1Rh_1$	$OMNRh_2Rh_0$	$ANRh_1Rh_1$ ♀		
70	A_2MNRh_1rh	OMNrh	$OMRh_1rh$ ♀		
71	A_1MNrh	$OMNRh_0$	$AMNRh_0$ ♂		
72	$ONRh_1Rh_1$	OMrh	$OMNRh_1rh$		
73	$ONRh_2Rh_2$	A_1MNrh	A_1MNRh_2 ♀		
74	$OMRh_2Rh_0$	OMNrh	$OMNRh_1rh$ ♂		
75	$OMNRh_1rh$	OMNrh	$OMRh_1rh$ ♂	$OMNRh_1rh$ ♀	
76	$OMRh_1Rh_1$	A_1MNrh	A_1MNRh_1rh ♂		
77	A_2MNRh_2	OMNrh	A_2MNrh ♂	A_2Mrh ♂	
78	A_1MRh_1rh	BMrh′rh	A_1BMrh ♀	BMrh′rh ♂	
79	$BNRh_2$	OMNrh	$BMNRh_2$ ♂	BNrh ♀	
80	$OMRh_2rh$	$A_2BMNRh_1Rh_1$	A_2MNRh_1rh		
81	$A_2MNRh_2Rh_0$	A_1MNrh	A_1MRh_2 ♀		
82	BMNrh	$OMNRh_1Rh_1$	$BMRh_1rh$ ♂	$BMNRh_1rh$♂	
83	$OMRh_1rh$	A_1Mrh	A_1Mrh ♀		
84	$BMNRh_1Rh_1$	$A_1MNrh′rh$	$OMNRh_1Rh_1$ ♀		
85	A_2BMNRh_2	$OMNRh_2rh$	$BMNRh_2$ ♂	$BMNRh_2$ ♂	
86	$BMNRh_2rh$	OMrh	$OMRh_2rh$ ♀	$BMNRh_2rh$	
87	$ONRh_1Rh_1$	A_1Mrh	A_1MNRh_1rh		
88	$A_1BMRh_1Rh_1$	A_2MNrh	A_2BMNRh_1rh ♂		
89	$BNRh_1Rh_1$	$OMNRh_1Rh_1$	$BNRh_1Rh_1$		
90	$ONRh_1Rh_1$	BMrh	$OMNRh_1rh$ ♀	$BMNRh_1rh$ ♀	
91	$OMNRh_2Rh_0$	A_2MNrh	$OMNRh_1rh$ ♂		
92	$A_1MNRh_2Rh_0$	$OMNRh_2rh$	A_1MNRh_2rh ♂	$OMNRh_2rh$ ♀	$ONRh_2Rh_0$ ♀
93	$ONRh_2Rh_2$	A_1MRh_2rh	$A_1MNRh_2Rh_2$ ♀		

TABLE 2.—*Continued*

FAMILY NO.	FATHER	MOTHER	CHILDREN		
94	$OMRh_1Rh_1$	$A_1BMNRh_1Rh_1$	$A_1MNRh_1Rh_1$ ♂		
95	$OMRh_1rh$	OMNrh	$OMNRh_1rh$ ♂	OMNrh	
96*	$OMRh_2Rh_0$	$BMNRh_1rh$	$BMRh_2Rh_0$ ♀	$BMRh_2Rh_0$ ♀	$OMRh_2$ ♀
97	A_1MNRh_1rh	BMrh	OMNrh ♂	$BMRh_1rh$ ♂	
98	$OMNRh_2rh$	$A_2MNrh''rh$	$ONrh''rh$ ♀	$A_2MRh_2Rh_2$ ♀	$ONrh''$ ♂
99	$A_1MRh_1Rh_1$	ONrh	A_1MNRh_1rh		
100	$A_1MNRh_1Rh_1$	ONrh	$ONRh_1rh$ ♂		
101	$A_1NRh_1Rh_1$	A_1Mrh	$OMNRh_1rh$ ♀	A_1MNRh_1rh ♂	
102	$ONRh_1rh$	$A_1Mrh'rh$	OMNrh ♂		
103	$BMNRh_1Rh_1$	A_1Mrh	A_1BMRh_1rh ♀	$ABMRh_1rh$ ♂	
104	$OMRh_2$	OMNrh	OMNrh ♂		
105	$A_2MNRh_2Rh_0$	$OMNRh_1Rh_1$	$A_2MNRh_2Rh_0$ ♀	$A_2NRh_2Rh_0$ ♂	$OMNRh_1Rh_1$ ♂
106	$OMRh_1Rh_1$	A_1Mrh	A_1MRh_1rh ♀	A_1MRh_1rh ♂	
107	$ONRh_2rh$	A_1MNrh	ONrh ♂	A_1NRh_2rh ♀	$ONRh_2rh$ ♀
108	A_1NRh_1rh	A_1MNrh	A_1NRh_1rh ♂		
109	A_1MNRh_0	ONrh	$OMNRh_0$ ♂	OMNrh ♀	A_1Nrh
110	$ONRh_1Rh_1$	A_1Mrh	A_2MNRh_1rh ♂	$AMNRh_1rh$ ♂	
111	$ONRh_2$	A_1MNrh	$OMNRh_2$ ♂	OMNrh ♂	$OMNRh_2$
112	$A_1MRh_2Rh_0$	OMNrh	A_1MNRh_1rh ♀	A_1MRh_2rh ♂	$AMNRh_2$ ♂
113	$A_1MRh_2Rh_0$	A_1Nrh	$AMNRh_1rh$ ♀		
114	A_1BMRh_0	BMNrh	$BMRh_0$ ♀		
115	$OMRh_1rh$	OMrh	$OMRh_0$ ♂		
116	$A_1MRh_1Rh_1$	$OMNRh_1rh$	A_1MRh_1rh ♀		
117	A_1Mrh	$ONRh_1Rh_1$	A_1MNRh_1rh ♀	$OMNRh_1rh$ ♂	A_1MNRh_1rh ♀
			A_1MNRh_1rh ♂	A_1MNRh_1rh ♀	
118	$A_1MNRh_1Rh_1$	$OMRh_1rh$	A_1MRh_1rh ♀		
119	$ONRh_1rh$	OMNrh	ONrh ♀		
120	$A_1MRh_1Rh_1$	OMrh	$OMRh_1rh$ ♂		
121	$A_1MRh_1Rh_1$	A_1Mrh	A_1MRh_1rh ♂	A_1MRh_1rh ♂	
122	$A_1MNRh_1Rh_1$	$OMNRh_1Rh_1$	$OMNRh_1Rh_1$		
123	$A_1NRh_1Rh_1$	$A_1MRh_1Rh_1$	$A_1MNRh_1Rh_1$ ♂	$A_1MNRh_1Rh_1$ ♀	
124	$OMNRh_2rh$	BNrh	$OMNRh_2rh$ ♀	$OMNRh_2rh$ ♀	$BMNRh_2rh$ ♂
125	ONrh	A_1BMrh	BMNrh ♂		
126	A_2MRh_1rh	A_1MRh_1rh	A_1MRh_1rh ♂		
127	$A_1MNRh_1Rh_1$	A_1Nrh	A_1NRh_1rh ♀		
128	$A_1NRh_2Rh_0$	$ONRh_1Rh_1$	$A_1NRh_2Rh_0$ ♀		
129	$OMNRh_1Rh_1$	A_1Mrh	$OMNRh_1rh$ ♂		
130	$OMRh_2rh$	OMNrh	$OMNRh_2rh$ ♂		
131	$ONRh_1rh$	OMrh	$OMNRh_1rh$ ♀	OMNrh ♀	OMNrh
132	A_1NRh_2rh	BMNrh	$OMNRh_2rh$ ♀	AMNrh ♂	
133	$ONRh_1rh$	ONrh	$ONRh_1rh$ ♀		
134	$OMNRh_0$	A_1MNrh	$OMRh_0$ ♂		
135	$OMRh_1rh$	A_1MNrh	A_1Mrh ♀		
136	A_1BMRh_1rh	$OMNRh_1rh$	A_1MRh_1rh ♀	A_1Mrh ♂	
137	A_1NRh_1rh	OMrh	OMNrh ♂		
138	$OMRh_1Rh_1$	A_1MNrh	A_1MRh_1rh ♂	$OMRh_1rh$ ♀	
139	$OMNRh_1rh$	OMrh	OMrh ♂		

TABLE 2.—*Continued*

FAMILY NO.	FATHER	MOTHER	CHILDREN		
140	$OMRh_1rh$	A_1MNrh	A_1Mrh ♀		
141	A_1BMRh_1rh	A_1MNrh	$BMNRh_1rh$ ♂	A_1BMNRh_1rh	
142	$BMNRh_2rh$	$ONrh$	$BMNrh$ ♂	$BNRh_2rh$ ♂	$OMNrh$
143	$A_1MNRh_2Rh_0$	$A_2MNrh'rh$	$A_1MNRh_2Rh_0$ ♂		
144	A_1NRh_1rh	$OMNrh$	$ONRh_1rh$ ♂		
145	$OMNRh_2Rh_0$	A_2MNrh	$OMRh_1rh$ ♂	A_2NRh_2rh ♂	$OMNRh_2$ ♂
146	$A_2NRh_2Rh_0$	A_1Nrh	$ANRh_1rh$		
147	A_1MRh_2rh	A_1MNrh	A_1MNrh ♂		
148	A_2MRh_1rh	A_1MNrh	A_2MNRh_1rh ♂		
149	A_1NRh_0	$OMrh$	A_1MNRh_0 ♂		
150	$OMRh_1rh$	$OMNrh$	$OMRh_0$ ♀		
151	A_1NRh_1rh	$ONrh$	A_1Nrh ♀		
152	A_2BMNRh_1rh	A_1MNrh	$ANRh_1rh$ ♂		
153	A_1MNRh_1rh	A_1Mrh	$OMNRh_1rh$ ♀	A_1MRh_1rh	
154	A_1NRh_1rh	A_1MNrh	A_1NRh_1rh ♀		
155†	$ONRh_1Rh_1$	$BMNrh$	$OMNRh_1rh$ ♂		
156†	A_1MNRh_1rh	A_2BMNrh	A_1NRh_1rh ♀		
157†	$OMRh_1rh$	A_1MNrh	$OMRh_0$ ♂		
158†	$BMNRh_1^wRh_1$	$OMNrh$	$OMRh_1^wrh$ ♀		
159†	$A_1MNRh_2Rh_0$	$BMNrh$	$AMNRh_2rh$ ♂		
160†	$A_2MNRh_1Rh_1$	$ONrh$	A_2MNRh_1rh ♂	A_2MNRh_1rh ♂	A_2MNRh_1rh ♂
161†	$A_2NRh_2Rh_0$	A_1Nrh	A_1NRh_2rh ♀ A_1NRh_1rh ♂	A_1NRh_2rh ♀	A_1NRh_1rh ♀
162†	$A_1BMNRh_1Rh_1$	$OMNrh$	$BMRh_1rh$ ♀		
163†	$OMNRh_2Rh_0$	$BMrh$	$OMNRh_1rh$ ♀	$BMNRh_2rh$ ♂	$OMNRh_2rh$ ♀
164†	A_1BMNRh_1rh	A_1MNrh	$ABMNRh_1rh$ ♀		
165†	$BMNRh_1rh$	$A_1MNRh_1Rh_1$	A_1BMNRh_1rh		
166†	$BMNRh_1rh$	$OMrh$	$OMRh_1rh$ ♂		
167†	$BMRh_1Rh_1$	$OMNrh$	$BMNRh_1rh$ ♀		
168†	$BMRh_1rh$	$OMNrh$	$BMNRh_1rh$ ♀		
169†	$OMNRh_2rh$	$BMrh$	$OMRh_2rh$ ♀		
170†	$OMNRh_2Rh_0$	$BMNrh$	$BMNRh_1rh$ ♂		
171†	$A_1BMNRh_1Rh_1$	$ONrh$	A_1NRh_1rh ♂		
172†	$BMNRh_1Rh_1$	$ONrh$	$BMNRh_1rh$ ♀		
173†	$BMRh_2rh$	$OMNRh_2rh$	$BMNRh_2rh$ ♂		
174†	$OMRh_0$	A_1Mrh	$OMRh_0$ ♂	A_1MRh_0 ♂	
175†	$A_1MNRh_2Rh_0$	A_1Nrh	$OMNRh_2rh$ ♂	$OMNRh_1rh$	
176†	$OMNRh_2rh$	A_1MNrh	$ONrh$ ♀ $ONrh$ ♂	A_1MNRh_2rh ♂ A_1NRh_2rh ♀	$OMNRh_2rh$ ♀
177†	A_2MNRh_0	A_1MNrh	A_1Mrh ♂		
178†	$ONRh_1Rh_1$	$ONrh$	$ONRh_1rh$ ♂		
179†	A_2MNRh_2rh	$A_1MNrh''rh$	$A_1MRh_2Rh_2$ ♂		
180†	$OMRh_2Rh_2$	$BMNRh_2Rh_1$	$OMRh_2Rh_2$ ♂	$BNRh_2Rh_2$ ♂	
181†	$OMNRh_2Rh_0$	$OMNrh$	$OMRh_1rh$ ♀		
182†	$OMNRh_1Rh_1$	$ONrh$	$ONRh_1rh$ ♀	$ONRh_1rh$ ♂	
183†	$OMNRh_1Rh_1$	A_1Nrh	A_1MNRh_1rh ♀ A_1NRh_1rh ♂	A_1MNRh_1rh ♂	A_1NRh_1rh ♀

TABLE 2.—*Continued*

FAMILY NO.	FATHER	MOTHER	CHILDREN	
184†	$OMNRh_1Rh_1$	A_2MNrh	$OMNRh_1rh$ ♀	
185†	A_1MNRh_1rh	A_1Mrh	A_1MRh_1rh ♂	
186†	$OMRh_1Rh_1$	OMrh	$OMRh_1rh$ ♂	
187†	$A_2NRh_1Rh_1$	A_1Nrh	$ONRh_1rh$ ♂	
188†	$OMRh_1Rh_1$	A_1Mrh	A_1MRh_1rh	
189†	$A_1MNRh_1Rh_1$	$BNRh_2rh$	$OMNRh_2Rh_0$ ♂	
190†	$OMRh_1rh$	$A_1Nrh'rh$	$OMNRh_0$	$AMNRh_1Rh_1$ ♂
191†	$A_1MNRh_2Rh_0$	BNrh	$ONRh_1rh$ ♂	$BNRh_1rh$ ♂
192†	$A_1NRh''Rh_1$	OMrh	A_1MNRh_1rh ♀	
193†	$ONRh_1rh$	A_1MNrh	OMNrh ♂	$OMNRh_1rh$ ♂
194†	$A_1MNRh_2Rh_0$	OMNrh	A_1MNRh_2rh ♂	
195†	$OMNRh_1Rh_1$	ONrh	$ONRh_1rh$ ♂	$ONRh_1rh$ ♀
196†	$OMNRh_1rh$	ONrh	ONrh ♂	
197†	A_1MNRh_1rh	A_2MNrh	A_2MNRh_1rh ♂	
198†	$A_1MRh_1Rh_1$	BMNrh	A_1BMRh_1rh ♂	
199†	$OMNRh_1Rh_1$	OMNrh	$ONRh_1rh$ ♂	$OMNRh_1rh$
200†	A_1MNRh_1rh	OMrh	A_1MNrh ♀	

* Bracketed children are twins.

† In these families all bloods were tested with anti-rh^w serum.

‡ In this family, the Rh type of the child does not satisfy the genetic predictions.

be considered homozygous for the Rh_0 factor. In the latter case, if the type rh wife is very highly sensitized to the Rh_0 factor, further pregnancies would be futile because all would terminate in stillbirths.

As will be seen, the International Rh-Hr Nomenclature has been particularly valuable for purposes of clarity in the presentation of the results of the present study, because some of the rarer antisera (anti-hr″ and anti-rh^w) were not available at all times. The notations of the phenotypes make clear when the anti-hr″ serum was used and when it was not. For example, when hr″ tests were not performed, bloods are classified as Rh_2 and rh″, etc. (cf. families 53, 65, 66, 67); when tests with anti-hr″ were made, type Rh_2 bloods could be further subdivided into types Rh_2Rh_2 and Rh_2rh, depending whether the reactions with this serum were negative or positive. Similarly, when type Rh_1Rh_2 bloods were also clumped by anti-hr′ and anti-hr″ sera, such bloods were designated Rh_zRh_0.

RESULTS

The findings in our new series of 200 families are presented in table 2. There is only a single contradiction to the genetic theory of the Rh-Hr blood types, namely, family ✱14. In this case, the mother belongs to type rh, the father to type Rh_1rh, the first child to type rh, while the second child belongs to type Rh_2rh. Thus, the second child possessed the rh″ factor which is lacking from

TABLE 3. PHENOTYPES AND GENOTYPES IN SELECTED FAMILIES

FAMILY NUMBER		FATHER	MOTHER	CHILDREN			
3	Phenotype	Rh_1Rh_1	rh	1) Rh_1rh	2) Rh_1rh	3) Rh_1rh	
	Genotype	R^1R^1 or R^1r'	rr	R^1r	R^1r	R^1r	
8	Phenotype	Rh_1Rh_1	rh	1) Rh_1rh	2) rh′rh	3) Rh_1rh	
	Genotype	R^1r'	rr	R_1r	$r'r$	R^1r	
7	Phenotype	Rh_2Rh_0	rh	1) Rh_2rh	2) rh′rh		
	Genotype	R^2r'	rr	R^2r	$r'r$		
161	Phenotype	Rh_2Rh_0	rh	1) Rh_2rh	2) Rh_2rh	3) Rh_1rh	4) Rh_1rh
	Genotype	R^1R^2	rr	R^2r	R^2r	R^1r	R^1r
35	Phenotype	Rh_2Rh_1	rh	1) Rh_2Rh_0	2) Rh_2Rh_0		
	Genotype	R^2R^1 or R^2r'	rr	R^2r	R^2r		
55	Phenotype	Rh_1rh	rh	1) Rh_1rh	2) rh	3) Rh_1rh	
	Genotype	R^1r	rr	R^1r	rr	R^1r	
54	Phenotype	Rh_1rh	rh	1) Rh_0	2) Rh_1rh		
	Genotype	R^1R^0	rr	R_0r	R^1r		
190	Phenotype	Rh_1rh	rh′rh	1) Rh_0	2) Rh_1Rh_1		
	Genotype	R^1R^0	$r'r$	R^0r	R^1r'		
59	Phenotype	Rh_1Rh_1	rh′rh	1) Rh_1Rh_1	2) Rh_1rh		
	Genotype	R^1R^1 or R^1r'	$r'r$	R^1r'	R^1r		
158	Phenotype	$Rh_1^wRh_1$	rh	1) Rh_1^wrh			
	Genotype	$R^{1w}R^1$, $R^{1w}R^{1w}$, or $R^{1w}r'$	rr	$R^{1w}r$			
165	Phenotype	Rh_2Rh_0	Rh_1Rh_1	1) Rh_2Rh_0	2) Rh_2Rh_0	3) Rh_1Rh_1	
	Genotype	R^1R^2, R^1r'', or R^2r'	R^1R^1 or R^1r'	R^1R^2, R_1r'', or R^2r'	R^1R^2, R^1r'', or R^2r'	R^1R^1 or R^1r'	
180	Phenotype	Rh_2Rh_2	Rh_2Rh_1	1) Rh_2Rh_2	2) Rh_2Rh_2		
	Genotype	R^2R^2, or R^2r''	R^2R^1, R^2r', or R^1r^y	R^2R^2, R^2r'', or R^2r^y	R^2R^2, R^2r'', or R^2r^y		

the bloods of the supposed parents. This apparent exception to the genetic theory can be attributed to illegitimacy, which is bound to turn up occasionally in extensive studies of this nature. The table contains no contradictions to the laws of heredity of the A-B-O blood groups or the M-N types.

Some of the families involve rather unusual combinations of the Rh types and merit more detailed discussion. In family #7, the father belongs to type Rh_2Rh_0, the mother to type rh and the first child to type Rh_2rh, the second child to type rh′rh. Since the mother has the genotype *rr*, she will transmit an

TABLE 4. HEREDITY OF THE RH TYPES INCLUDING THE hr′ AND hr″ FACTORS, IN FAMILIES OF TABLE 2

PARENTAL COMBINATION	NUMBER OF FAMILIES	NUMBER OF CHILDREN OF TYPE												TOTALS
		rh	Rh_1		Rh_2			Rh_1Rh_2		Rh_0	rh′rh	rh″		
			Rh_1rh	Rh_1Rh_1	Rh_2	Rh_2rh	Rh_2Rh_2	Rh_2Rh_0	Rh_2Rh_1			rh″	rh′rh	
rh × rh	3	3	0	0	0	0	0	0	0	0	0	0	0	3
rh × Rh_1rh	50	30	38	0	0	(1)	0	0	0	4	0	0	0	73
rh × Rh_1Rh_1	51	0	83	0	0	0	0	0	0	0	1	0	0	84
rh × Rh_2	6	6	0	0	5	0	0	0	0	0	0	0	0	11
rh × Rh_2rh	14	11	0	0	2	16	0	0	0	0	0	0	0	29
rh × Rh_2Rh_2	2	0	0	0	1	2	0	0	0	0	0	0	0	3
rh × Rh_2Rh_0	18	0	14	0	4	12	0	3	0	0	0	0	0	33
rh × Rh_2Rh_1	2	0	1	0	0	0	0	0	0	0	1	0	0	2
rh × Rh_0	9	3	0	0	0	0	0	0	0	9	0	0	0	12
Rh_1rh × Rh_1rh	3	1	3	0	0	0	0	0	0	0	0	0	0	4
Rh_1rh × Rh_1Rh_1	9	0	6	4	0	0	0	0	0	0	0	0	0	10
Rh_1Rh_1 × Rh_1Rh_1	4	0	0	5	0	0	0	0	0	0	0	0	0	5
Rh_1Rh_1 × Rh_2rh	2	0	1	0	0	0	0	1	0	0	0	0	0	2
Rh_1rh × Rh_2Rh_0	4	0	2	2	1	0	0	3	0	0	0	0	0	8
Rh_1Rh_1 × Rh_2Rh_0	4	0	0	3	0	0	0	3	0	0	0	0	0	6
Rh_2 × Rh_2rh	1	0	0	0	2	0	0	0	0	0	0	0	0	2
Rh_2rh × Rh_2rh	1	0	0	0	0	1	0	0	0	0	0	0	0	1
Rh_2Rh_2 × Rh_2rh	1	0	0	0	0	0	1	0	0	0	0	0	0	1
Rh_2rh × Rh_2Rh_0	1	0	0	0	0	2	0	1	0	0	0	0	0	3
Rh_2rh_2 × Rh_2Rh_1	1	0	0	0	0	0	0	0	2	0	0	0	0	2
Rh_2Rh_0 × Rh_2Rh_0	3	0	0	1	1	0	0	2	0	0	0	0	0	4
rh′rh × Rh_1rh	3	2	0	1	0	0	0	0	0	1	1	0	0	5
rh′rh × Rh_1Rh_1	2	0	1	2	0	0	0	0	0	0	0	0	0	3
rh′rh × Rh_2rh	1	0	0	0	0	0	0	0	0	0	3	0	0	3
rh′rh × Rh_2Rh_0	1	0	0	0	0	0	0	1	0	0	0	0	0	1
rh″ × Rh_1Rh_1	1	0	1	0	0	0	0	0	0	0	0	0	0	1
rh″rh × Rh_2rh	2	0	0	0	0	0	2	0	0	0	0	1	1	4
rh′rh″ × Rh_2	1	0	0	0	1	0	0	1	0	0	0	0	0	2
Totals	200	56	150	18	17	34	3	15	2	14	6	1	1	317

r gene to each child so that the genotypes of the children must be R^2r and $r'r$, respectively. The genes R^2 and r' must have come from the type Rh_2Rh_0 father whose genotype must therefore be R^2r'. More commonly individuals of phenotype Rh_2Rh_0 belong to genotype R^1R^2 so that when wedded to type rh women half of the offspring are type Rh_1 and half are type Rh_2 (see families 112, 161, 163 and 175). Other illustrative families are listed in table 3 in order to demon-

strate how to derive the genotypes from the phenotypes with the aid of the distribution of the Rh types in the families. The families have been selected especially to demonstrate how different individuals of the same phenotype need not necessarily belong to the same genotype even when members of the same family. For example, in family # 54 of table 2, the father and second child both belong to phenotype Rh_1rh, yet the father belongs to genotype R^1R^0 and

TABLE 5. SUMMARY OF AUTHORS' HEREDITY STUDIES ON THE EIGHT RH BLOOD TYPES TO DATE

PARENTAL COMBINATION	NUMBER OF FAMILIES	NUMBER OF CHILDREN OF TYPE								TOTALS
		rh	Rh_1	Rh_2	Rh_1Rh_2	Rh_0	rh′	rh″	rh′rh″	
rh × rh	23	42	0	0	0	0	0	0	0	42
rh × Rh_1	374	113	470	(1)	0	25	4	0	0	613
rh × Rh_2	88	54	0	93	0	2	0	0	0	149
rh × Rh_1Rh_2	103	2	84	76	5	0	1	0	0	168
rh × Rh_0	19	8	0	0	0	21	0	0	0	29
rh × rh′	3	1	0	(1)	0	0	2	0	0	4
rh × rh″	2	2	0	0	0	0	0	5	0	7
rh × rh′rh″	1	1	0	0	0	0	0	0	1	2
Rh_1 × Rh_1	96	11	150	0	0	6	1	0	0	168
Rh_1 × Rh_2	43	11	28	12	21	2	3	0	0	77
Rh_1 × Rh_1Rh_2	63	0	72	13	49	0	1	0	0	135
Rh_1 × Rh_0	14	6	11	0	0	3	0	0	0	20
Rh_1 × rh′	20	6	17	0	0	1	5	0	0	29
Rh_1 × rh″	10	3	6	0	6	0	0	0	0	15
Rh_2 × Rh_2	8	2	0	10	0	0	0	0	0	12
Rh_2 × Rh_1Rh_2	17	0	8	17	11	0	0	0	0	36
Rh_2 × Rh_0	3	0	0	2	0	4	0	0	0	6
Rh_2 × rh′	6	1	0	2	3	0	5	0	0	11
Rh_2 × rh″	2	0	0	2	0	0	0	2	0	4
Rh_2 × rh′rh″	1	0	0	1	1	0	0	0	0	2
Rh_1Rh_2 × Rh_1Rh_2	13	0	5	4	8	0	0	0	0	17
Rh_1Rh_2 × Rh_0	3	0	2	1	0	0	0	0	0	3
Rh_1Rh_2 × rh′	5	0	3	1	4	0	0	0	0	8
Rh_1Rh_2 × rh″	2	0	1	0	1	0	0	0	0	2
Rh_0 × Rh_0	1	0	0	0	0	1	0	0	0	1
Rh_0 × rh′	2	0	2	0	0	1	1	0	0	4
Rh_0 × rh′rh″	1	0	0	0	0	0	0	3	0	3
Totals.....	923	263	859	236	109	66	23	10	1	1,567

the child to genotype R^1r. Family # 180 is of particular interest because it illustrates the transmission of the rare gene R^z.

In table 4, the results of the Rh tests listed in table 2 have been summarized, except that the families also tested for the rh^w factor are not indicated. With a single exception mentioned above, the results fit well with the expectations under the theory of multiple allelic genes. In fact, for the past few years we have been applying the Rh-Hr tests routinely alongside of the A-B-O and M-N

tests in medicolegal cases of disputed parentage. In material such as that presented here, occasional contradictions to the theory are to be expected due to illegitimacy, so perhaps the best test for the genetic theory is derived from mother-child combinations. Thus, according to the genetic theory, rh′-negative mothers cannot have hr′-negative children; nor can hr′-negative mothers have rh′-negative children. Not a single exception to this law has been encountered in our family material to date, nor has an exception turned up in

TABLE 6. DOUBLE EXCLUSION OF PATERNITY BY A-B-O AND RH-HR TESTS

BLOOD OF	GROUP AND SUBGROUP	M-N TYPE	RH-HR TYPE
Putative father	A_2	MN	$Rh_1^{w}rh$
Mother	O	MN	Rh_2rh
Child	B	N	Rh_1rh

TABLE 7. HEREDITY OF THE BLOOD GROUPS AND SUBGROUPS IN THE FAMILIES OF TABLE 2

PARENTAL COMBINATION	NUMBER OF FAMILIES	NUMBER OF CHILDREN OF GROUP									TOTAL
		O	A				B	AB			
			A_1	A_2	A	$A_{1,2}$		A_1B	A_2B	AB	
O × O	30	46	0	0	0	0	0	0	0	0	46
O × A_1	60	38	50	3	8	1	0	0	0	0	100
O × A_2	13	14	0	13	0	0	0	0	0	0	27
O × B	28	22	0	0	0	0	24	0	0	0	46
O × A_1B	7	0	6	0	0	0	3	0	0	0	9
O × A_2B	3	0	0	2	0	0	2	0	0	0	4
A_1 × A_1	16	6	17	0	2	0	0	0	0	0	25
A_1 × A_2	14	3	10	3	1	0	0	0	0	0	17
A_1 × B	17	6	3	0	2	0	5	8	0	2	26
A_1 × A_1B	4	0	2	0	0	0	1	2	0	1	6
A_1 × A_2B	2	0	1	0	1	0	0	0	0	0	2
A_2 × B	1	0	0	0	0	0	1	0	0	0	1
A_2 × A_1B	1	0	0	0	0	0	0	0	1	0	1
B × A_1B	3	0	0	0	0	0	4	0	0	0	4
A_1B × A_1B	1	0	1	0	0	0	0	1	0	1	3
Totals	200	135	90	21	14	1	40	11	1	4	317

more than 500 medicolegal cases of disputed parentage. Similarly, in a shorter series of mother-child combinations, no exception has been found to the law that rh″-negative parents cannot have hr″-negative children; and hr″-negative parents cannot have rh″-negative children. The medicolegal investigations will be the subject for a future communication.

While Hr antisera were not readily available until 1945, all families since 1943 have been tested for the eight Rh types. It seems of interest, therefore, to combine our new results with our previous findings as has been done in table 5.

As shown in the table, our studies to date include 923 families with 1567 children. Thus, the family and statistical data which we have presented in this and previous papers in support of the theory of multiple allelic Rh genes are considerably greater than the evidence submitted when the genetic theories of the A-B-O and M-N types were considered acceptable.

The discovery of the rh^w factor has increased only slightly the chance of excluding paternity where the defendant in a paternity case has been falsely accused. However, one interesting case has already been encountered and this is presented in table 6. Since the mother in this case belongs to type Rh_2 and the child to type Rh_1, the putative father had to carry either the r' or R^1 genes. Although the putative father belongs to type Rh_1, he could not carry either the R^1 or r' gene because he belongs to subtype $Rh_1^{w}rh$ and is therefore a carrier of the R^{1w} gene instead. Significantly, the putative father is excluded also because he belongs to group A, the mother to group O, and the child to group B.

TABLE 8. HEREDITY OF THE M-N TYPES IN THE FAMILIES OF TABLE 2

PARENTAL COMBINATION	NUMBER OF FAMILIES	NUMBER OF CHILDREN OF TYPE			TOTALS
		M	N	MN	
M × M	18	24	0	0	24
M × N	22	0	0	38	38
N × N	9	0	14	0	14
MN × M	50	38	0	34	72
MN × N	45	0	33	47	80
MN × MN	56	26	18	44	88
Totals	200	88	65	163	316

Our new family data have been summarized from the standpoint of heredity of the A-B-O groups and M-N types in tables 7 and 8. As has already been mentioned, the findings show no contradictions to the established laws of heredity of the A-B-O groups and the M-N types.

SUMMARY AND CONCLUSIONS

New investigations on the heredity of the A-B-O blood groups and subgroups, the M-N types, and the Rh-Hr types in a new series of 200 families with 317 children are described. To date a total of 923 families with 1567 children have been tested by the authors for the eight Rh types and only two contradictions to the theory of multiple allelic Rh genes have been encountered, both due to illegitimacy. Thus, the findings agree well with the theoretical expectations and fully justify the medicolegal application of the Rh-Hr tests in cases of disputed parentage.

The discovery of the rh^w factor has increased the number of fully identified

Rh genes to nine. Because of its relative rarity, the rh^w factor only slightly increases the chances of excluding parentage for men who are falsely accused of paternity.

The investigations on the heredity of the Rh-Hr types and their serology have made possible a simple and logical International Nomenclature for the Rh-Hr types such as already exists for the A-B-O groups and M-N types.

REFERENCES

CALLENDER, S. T., & RACE, R. R. 1946. A serological and genetical study of multiple antibodies formed in response to blood transfusion by a patient with lupus erythematosus diffusus. *Ann. Eugen.*, Cambr. 13: 102–117.

HABERMAN, S., HILL, J. M., EVERIST, B. W., & DAVENPORT, J. W., JR. 1948. The demonstration and characterization of the anti-d agglutinin and antigen predicted by Fisher and Race. *Blood*, Balt. 3: 682–788.

RACE, R. R., SANGER, R., & LAWLER, S. D. 1948. Allelomorphs of the Rh genes C. *Heredity*, 2: 237–240.

SONN, E. B., & WIENER, A. S. 1945. Heredity of the Rh blood types. III. Observations on the rare genes *Rh'* and *Rh''*. *J. Hered.* 36: 301–304.

UNGER, L. J. & WIENER, A. S. 1949. Observations on the racial distribution of variants of the blood type rh'. *Proc. Soc. Exp. Biol.*, N. Y. 70: 629–630.

WIENER, A. S. 1944. The Rh series of allelic genes. *Science*, 100: 595–597.

WIENER, A. S. 1949*a*. Heredity of the Rh blood types. VII. Additional family studies, with special reference to the genes R^z and r^v. *Hereditas*, 35(Supp.): 500–519.

WIENER, A. S. 1949*b*. An Rh glossary. *Bull. Dade Co. M. Ass.* 20: 20–32.

WIENER, A. S., DAVIDSOHN, I., & POTTER, E. L. 1945. Heredity of the Rh blood types. II. Observations on the relation of factor Hr to the Rh blood types. *J. Exp. Med.* 81: 63–72.

WIENER, A. S., & GORDON, E. B. 1949. Studies on the blood factor rh^w. *Am. J. Clin. Path.* 19: 621–629.

WIENER, A. S., & SONN, E. B. 1945. Heredity of the Rh blood types. IV. Medico-legal applications in cases of disputed parentage. *J. Laborat. Clin. Med.* 30: 395–404.

WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1944. Heredity of the Rh blood types. *J. Exp. Med.* 97: 235–253.

WIENER, A. S., SONN, E. B., & POLIVKA, H. 1946. Heredity of the Rh blood types. V. Improved nomenclature; additional family studies with special reference to Hr. *Proc. Soc. Exp. Biol.*, N. Y. 61: 382–390.

WIENER, A. S., SONN-GORDON, E. B., & HANDMAN, L. 1947. Heredity of the Rh blood types. VI. Additional family studies, with special reference to the theory of multiple allelic genes. *J. Immun.*, Balt. 57: 203–214.

WIENER, A. S., UNGER, L. J., & MAZZARINO, C. A. 1949. Further studies on the rh^w factor. *Am. J. Clin. Path.* 19: 779–781.

Blood Types of Brazilian Indians
(Matto Grosso)

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AMERICAN Indians occupy a unique position in mankind with regard to the distribution of the various hereditary blood factors. For example, the frequency of group O generally exceeds 70 per cent among U. S. Indians, and not infrequently reaches 100 per cent among Central American and South American Indians. In contrast, the frequency of group O among most other peoples is less than 50 per cent, though in some, such as Indonesians, Melanesians, Filipinos, and Australian aborigines on the one hand, and in Eskimos and Icelanders on the other, values have been encountered ranging from 50 to 65 per cent.

In Brazil, observations have been made on tribes from the southern and northern extremes of the country. In Guaraní Indians of Rio Grande do Sul (Berardinelli & Roiter, 1934; Ribeiro, 1934) and in Tucano Indians of Alto Rio Negro, Amazonas (Biocca & Ottensooser, 1944), every individual tested belonged to group O. In Caïngangue Indians of Paraná (Fernandes, 1939), and in Canela Indians of Maranhão (da Silva, 1948), the frequency of group O reaches 92 to 93 per cent, the small difference from 100 per cent probably being due to slight racial admixture. The same interpretation may explain the similar percentage of group O among other North and South American tribes. It is obviously difficult to exclude mixing with other ethnic groups which had centuries to take place.

The predominance of type M among Indians is another well known feature, though investigations on the M-N types in Indians have been relatively scanty. Caucasians have about 30 per cent type M individuals, U. S. and Chilean Indians (Henckel *et al.*, 1941), about 60 per cent, while the incidence among North Brazilian Indians is intermediate (Biocca & Ottensooser, 1944; da Silva, 1948).

Only a few investigations on the Rh factor have been made in Indians, because sufficient quantities of antiserum have not become available until recently. The three main racial groups, Caucasoids, Negroids, and Mongoloids, are distinctly differentiated by the incidence of the Rh-negative type.[1] Most

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[1] An exceptional people are the Basques (Etcheverry, 1945, 1949; Chalmers *et al.*, 1948; Vaccaro *et al.*, 1948) with 30 to 35 per cent Rh-negatives and other peculiarities, such as low percentage of group B and lack of rh^w.

Caucasoids have 13 to 15 per cent Rh-negatives, Negroids 5 to 10 per cent, while Mongoloids have still lower frequencies, often zero. The incidence of Rh-negative individuals among Asiatic Indians (Greval & Roychowdhury, 1946; das Gupta, 1944; Khanolkar & Sanghvi, 1945; Ranganathan *et al.*, 1946), is 2 to 10 per cent, which is intermediate between Caucasoids and Mongoloids and similar to that of Negroids, from whom they deviate, however, with regard to the frequencies of the other Rh types. The frequency of Rh-negative individuals among Japanese was found to be 0.3 to 1.3 per cent (Waller & Levine, 1944; Miller & Taguchi, 1945; Pinkerton, 1944; Graydon & Simmons, 1945), among Chinese 0.7 and 1.5 per cent (Wiener, Sonn & Yi ,1944; Levine & Wong, 1943), among Filipinos 0.3 and 0 per cent (Simmons & Graydon, 1945; Pinkerton, 1944), and among Australian aborigines 0.2 per cent (Simmons, Graydon & Hamilton, 1946). In the following series of 200 or more individuals all were found to be Rh-positive: Maori (Graydon & Simmons, 1946), Fijians (Simmons, Graydon & Barnes, 1945), Hawaiians (Pinkerton, 1945), Papuans (Simmons, Graydon, Woods, Smith & Lancaster, 1946), Burmese (Mollison & Reddy, 1946), and Eskimos (Jordan, 1946).

In American Indians, similarly, the frequency of Rh-negatives is small or zero: 1 to 2 per cent in two series of 100 and 120 U. S. Indians, according to Landsteiner, Wiener, and Matson (1942) and Wiener, Hassler, *et al.*, respectively. The same low incidence was observed by Sandoval, Henckel and Givovich (1945) among 205 Chilean Mapuches. Moreover, among 98 Mexican Indians (Wiener, 1947; Wiener, Zepeda, Sonn & Polivka, 1945), and 104 U. S. Indians (Matson & Piper, 1947), all were Rh-positive. Summing up, American Indians are, with rare exceptions, all Rh-positive; in the cases where among 100 Indians a single Rh-negative individual is encountered it is difficult to exclude the possibility of more or less recent admixture with other races.

While the distributions of the A-B-O groups and of the M-N types are unique among American Indians, they do not enable one to classify Indians as Mongoloids; a better criterion of such a relationship is provided by the Rh-negative element. The latter is not the only serological indication, however, because the relationship of Indians to Mongoloids is also shown by the absence of subgroup A_2 and by the distribution of other Rh factors. These more refined differences will be discussed later.

MATERIAL AND METHODS

The preceding brief discussion shows how scanty have been the serological investigations on Indians in Brazil, where there are so many tribes of differing cultures. We had an opportunity to study the incidence of the blood factors in a considerable number of Brazilian Indians, when during the months of May to July of 1947 Dr. Ernani Martins da Silva made excursions to the south of Matto Grosso, where he studied Caiuá Indians in the frontier

regions of Paraguay, and Bororo Indians in the north in the São Lourenço Valley[2]. He sent us blood samples from these two tribes in six series, three from Caiuá Indians and three from Bororo Indians (table 1).

From Caiuá Indians (comprising one large and several small families) samples were taken in the following places:

1st series at the José Bonifácio Post (municipality of Ponta Porã).

2nd series at the Francisco Horta Post near the town Dourados.

3rd series at the Reserva Cerro Peron and the Benjamin Constant Post, near the place of Amambaí.

From the Bororo samples were taken in 3 villages within a period of 4 days:

1st series at Quejara.

2nd series at Colônia.

3rd series at Córrego Grande.

In both tribes there was a predominance of pure Indians; the few mixed Indians were easily recognized. Separation was carried out rigorously by inquiring concerning their ancestry, and by examining their somatic characteristics such as the color of the skin, color of the eyes, quality of the hair, slit of the eyelids, and manner of implantation of the lobe of the ear. Only individuals who passed all tests are included in the following statistics. The reliability of our method of selecting pure-bred Indians is confirmed (da Silva), by comparing the blood group distribution among Whites, Indians and mixed Indians in that region with the aid of the race mixture formula derived by one of us (Ottensooser, 1944). Venous blood was difficult to obtain from these Indians, so that finger puncture had to be employed. Several drops of blood were distributed among 2 or 3 capillary tubes which were put into numbered slips of paper.

Dr. Ernani Martins da Silva carried out tests for the common A-B-O blood groups and the Rh_0 factor on Bororo Indians and on the last series of Caiuá on the spot, in a makeshift laboratory at a post or in a "hotel". The capillaries were broken and placed into test tubes with a few drops of saline solution. Blood suspensions were obtained by shaking. The common blood grouping tests were carried out on slides. In the Rh tests, the tubes containing the mixture of serum and blood suspension were tied together, wrapped in cotton, and placed into a saucepan with water heated to 37°C by means of an alcohol burner. Readings were taken after ½ to 1 hour.

Our own examinations were made in São Paulo, 3 to 6 days after the blood specimens had been drawn. The blood samples were sent by air mail in a small wooden box, and arrived in good condition. Due to the low temperature (below 20°C) of the season hardly any specimens were spoiled. In order to prepare the blood suspensions, the capillaries were opened and placed into numbered tubes with 1 to 2 c.c. of saline solution and then centrifuged, in batches of about 40 at a time, for 15 minutes at about 1,500 r.p.m. This made the small clot come out of the capillaries producing a sediment in the tube. The supernatant fluid was siphoned off and saline added again to suspend the red cells. In rare cases, where centrifugation yielded no sediment, the capillaries were broken as described above. The 1 to 2 per cent blood suspensions were examined on the day of their preparation whenever possible.

The common blood groups were determined on slides or dishes with sera of groups O, A, and B. A few doubtful reactions, possibly due to changes in the blood sample during transportation, were checked further with group AB serum.

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[2] Our good friend, Dr. Ernani Martins da Silva, died a victim of his exploring zeal in December 1948, during an expedition in Goiaz.

To test for the M-N types, equal parts of blood suspension and serum (from Certified Blood Donor Service, N. Y. C.) were mixed; control tests with samples of known M-N types were also included. Readings were taken after 10 minutes with a hand lens.

For Rh typing we used anti-Rh_0 sera prepared by ourselves, and also anti-Rh_0, anti-rh′, and anti-rh″ sera kindly furnished by Dr. A. S. Wiener and by the Certified Blood Donor Service. For some of the latter sera we are obliged to Dr. Arnaldo Amado Ferreira. We are also indebted to Dr. J. M. Hill for supplying us with anti-hr′ serum. Tests with these sera were carried out by mixing, in small tubes, equal parts of diluted serum and blood suspensions, the first reading was taken after ½ to 1 hour of incubation at 37°C, and a second reading after keeping the tubes at room temperature (15°C to 20°C) for a few hours or overnight. Duplicate tests with sera of the same specificity always gave identical results.

TABLE 1. DISTRIBUTION OF THE BLOOD TYPES AMONG MATTO GROSSO INDIANS

TRIBE	SERIES NO.	NO. OBS.	GROUP O	NO. OBS.	Rh-POS.	NO. OBS.	Rh_1	Rh_2	Rh_1Rh_2 (Rh_3)	NO. OBS.	M	N	MN
Caiuá	1	89	89	89	89	89	23	17	49	88	68	1	19
	2	46	46	46	46	46	7	11	28	46	39	0	7
	3	102	102	38	38								
	Total	237	237	173	173	135	30	28	77	134	107	1	26
	%		100		100		22.2	20.7	57.1		79.9	0.7	19.4
Bororo	1	39	39	39	39	39	8	9	22				
	2	31	31	31	31	31	7	5	19				
	3	49	49	33	33	33	9	4	20				
	Total	119	119	103	103	103	24	18	61				
	%		100		100		23.3	17.5	59.2				

RESULTS

A-B-O System—Table 1 shows that the 237 Caiuá and 119 Bororo all belonged to group O. Also all other Matto Grosso Indians investigated at the same time invariably proved to be group O (da Silva). As already mentioned several South American tribes behave in this way, including Brazilian Indians.

M-N System—As shown in table 1, among the 134 Caiuá examined 79.9 per cent belonged to type M, 0.7 per cent to type N, and 19.4 per cent to type MN. As shown in table 2, these values satisfy the theoretical statistical requirements. Although based on a relatively small series of tests, the results are interesting. The percentage of type M is the highest observed among any Indians, and holds the second place in the world literature, the record still being retained by East Greenlanders (Fabricius-Hansen, 1939), who have 83.5 per cent type M, 0.9 per cent type N, and 15.6 per cent type MN.

Rh factor (*Tests with anti-Rh_0*)—As can be seen in table 1, the 173 Caiuá and 103 Bororo Indians tested were all Rh positive. The same results had been

obtained in a previous study on 165 Matto Grosso Indians (da Silva). Thus, in all, 441 Indians in that State tested with anti-Rh_0 serum proved to be Rh positive. These observations agree well with previous investigations on North American Indians.

Rh types—To our best knowledge, the incidence of the various Rh types among South American Indians has not been determined previously.

Since the frequencies found by us in Caiuá and Bororo do not differ beyond the limits of error (tables 1 and 3), the results may be combined. A little more than 20 per cent of 238 Indians belong to type Rh_1, almost the same incidence exists for type Rh_2 individuals, while Indians of type Rh_1Rh_2 constitute more than half of the total. Among these Indians, therefore there exists only the three types, Rh_1, Rh_2, and Rh_1Rh_2, while among an equal number of Whites, other types would also be found including dozens of type rh individuals, some Rh_0, and possibly representatives of the rare types rh′ and rh″.

TABLE 2. DISTRIBUTION OF THE M-N TYPES AMONG CAIUÁ INDIANS

NUMBERS OBSERVED				GENE FREQUENCIES		TEST OF BINOMALITY
Total (N)	M (a)	MN (b)	N (c)	$m = \frac{2a+b}{2N}$	$n = \frac{b+2c}{2N}$	$\chi^2 = \frac{N(b^2-4ac)^2}{(2a+b)^2(b+2c)^2}$
134	107	26	1	0.896	0.104	0.1825 D.F. = 1, $P = 0.67$

The fact that only three Rh types were found in this study simplifies the genetic analysis. Nevertheless, we must bear in mind that the absence of a serological type, even in a large material, does not necessarily exclude the presence of the corresponding gene in the population. Type rh, for example, was not encountered among the 441 Indians of Matto Grosso, and we therefore may estimate the frequency of this type as not exceeding 1 in 400; even so, the incidence of the corresponding gene r could be as high as 5 per cent, because $r = \sqrt{\text{rh}} \leqslant \sqrt{.002} \leqslant .05$. But when our observations are combined with those of other authors, the existence of gene r among pure Indians becomes improbable. Similarly, the other genes r', r'', r^y, and R^1, have not been detected serologically in our series of Indians. For this reason and others to be discussed later, these genes will not be taken into account in the following statistical analysis.

Therefore, we may assign to all the Indians of type Rh_1 the genotype R^1R^1 and to all the Indians of type Rh_2 the genotype R^2R^2. The calculated gene frequencies are given in table 3. The incidence of gene R^1 among Caiuá, for example, is obtained from the frequency of type Rh_1 as follows:

$$R^1 = \sqrt{R^1R^1} = \sqrt{\text{Rh}_1} = \sqrt{0.222} = 0.471$$

In the same manner, we obtain $R^2 = 0.456$. The sum $R^1 + R^2$ is less than unity or 100 per cent by the relatively high value of 7.3 per cent. In the Bororo, there is a corresponding shortage of 9.9 per cent. Since these two values (7.3 and 9.9 per cent) agree within the limits of statistical error for the two tribes, they are almost surely significant.

Wiener *et al.* (1947; 1945), had observed previously that among Mexican Indians there is a similar deficiency in the sum of the gene frequencies and explained it by postulating the existence of a third gene R^z in addition to R^1 and

TABLE 3. DISTRIBUTION OF THE RH TYPES AND OF THE CORRESPONDING GENES AMONG MATTO GROSSO INDIANS

TRIBE	NO. OBS.	PERCENTAGE OF TYPES			INCIDENCE OF GENES		
		Rh_1	Rh_2	Rh_1Rh_2 (Rh_z)	$R^1 = \sqrt{Rh_1}$	$R^2 = \sqrt{Rh_2}$	$R^z = (1-R^1-R^2)$
Caiuá	135	22.2	20.7	57.1	0.471	0.456	0.073
Bororo	103	23.3	17.5	59.2	0.483	0.418	0.099
Total	238	22.7	19.3	58.0	0.476	0.440	0.084

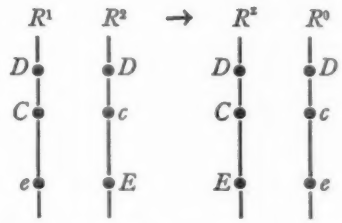
TABLE 4. RH PHENOTYPES AND GENOTYPES AMONG MATTO GROSSO INDIANS

PHENOTYPES	REACTIONS OF BLOOD CELLS WITH ANTISERA				GENOTYPES	FREQUENCY OBSERVED FOR PHENOTYPES Rh_1 AND Rh_2; COMPUTED IN THE OTHER CASES	
	rh′	Rh_0	rh″	hr′		Caiuá	Bororo
Rh_1	+	+	−	−	R^1R^1	0.222	0.233
Rh_2	−	+	+	+	R^2R^2	0.207	0.175
Rh_1Rh_2	+	+	+	+	$2\ R^1R^2$	0.430	0.404
					$2\ R^2R^z$	0.067	0.083
(Rh_z)	+	+	+	−	$2\ R^1R^z$	0.069	0.096
					R^zR^z	0.005	0.010

R^2. Our results support this interpretation. By introducing gene R^z into the calculations, as shown in table 4, results are obtained which are in accord with the genetic theory, while this is not true if one postulates the presence of other genes such as R^0 or r^y. Moreover, the hypothesis of the presence of gene R^z is supported by the results of tests with anti-hr′ serum.

Hr Factor (*Tests with anti-hr′ serum*). In the Bororo Indians, the blood type Rh_1Rh_2 (or Rh_z) has the frequency 0.592 or 59.2 per cent. This type can be subdivided, as shown in table 4, into four genotypes whose frequencies can be calculated. Two of these genotypes, R^1R^2 and R^zR^2 possess the factor hr′,

while the two other genotypes R^zR^z and R^zR^1, which together should have the incidence among type Rh_1Rh_2 Bororo Indians of 1.0 + 9.6 = 10.6 per cent, have no hr′. The existence of hr′-negative individuals of type Rh_1Rh_2 would be proof of the existence of gene R^z. The expected proportion of such individuals among type Rh_1Rh_2 Bororo Indians is 10.6:59.2 or approximately one in six. Tests were made with anti-hr′ serum on 12 Bororo of type Rh_1Rh_2, and one proved to be hr′ negative instead of the expected two such individuals. However, this is as good an agreement between calculation and observation as one could reasonably expect, the number of tests being very small due to the scar-



The CDE notations used by British workers are readily understood with the aid of the following equivalents:

Blood Factors		*Genetic Units*	
American nomenclature (Wiener)	British notations (Fisher-Race)	Genes	"Chromosomes"
		r	*cde*
Rh_0	D	r'	*Cde*
rh′	C	r''	*cdE*
rh″	E	r^y	*CdE*
Hr_0	d	R^0	*cDe*
hr′	c	R^1	*CDe*
hr″	e	R^2	*cDE*
		R^z	*CDE*

FIG. 1. HYPOTHESIS OF CROSSING-OVER ACCORDING TO R. A. FISHER

city of anti-hr′ serum. On the whole, therefore, the results corroborate the assumption of the presence of gene R^z in these Indians.

Gene analysis from the standpoint of the hypothesis of crossing-over. Fisher attempted to explain the Rh gene frequencies among the English by crossing-over. He postulated that in meiosis the common genotype R^1r would be able to form by exchange of the "elementary genes" D and d a small proportion of germ cells carrying the rare gene R^0 and r'. Similarly, by crossing-over, the common genotype R^2r could give rise to the rare genes R^0 and r'', while genotype R^1R^2 could give rise to genes R^0 and R^z (cf. Fig. 1). Therefore, R^0 would always originate whenever genes R^z or r' or r'' are formed, and in fact, in England the sum

of the frequencies of these last three genes approximately equals the frequency of R^0. Gene r^y would be expected to be extremely rare because it would have to be formed from a rare genotype such as R^2r' or R^1r''. However, Fisher's suggestion has not been confirmed serologically, so that one is justified in assuming that in the Rh gene complex the three postulated elementary genes are linked together permanently to form units. In practical cases of disputed paternity (Ottensooser & Versiani, 1949), the cross-over hypothesis can therefore be disregarded at the present stage of our knowledge.

Extensive family studies on the heredity of the Rh-Hr types have shown that crossing-over, if it occurs at all, must be extremely rare (Wiener, Belkin, & Sonn, 1944). For example, in the case of genotype R^1r, which is the most common in the United States, the formation of genes R^0 and r' has not yet been observed. A case explicable by crossing-over has been claimed recently by Glass (1948), but this single case is not conclusive because it can be explained far more reasonably on the basis of illegitimacy.

A further test of Fisher's hypothesis is provided by the results of serological-anthropological investigations. The Rh gene frequencies of various populations which we have calculated are summarized in table 6, but some of the series are too small to be of much value. On the whole, the results do not favor the crossing-over hypothesis, because the relations $R^0 = R^z$, or $R^0 = R^z + r' + r''$ do not hold, except in Mexican Indians where the frequencies of R^0 and R^z approximate one another.

In order to test whether the crossing-over hypothesis is supported by our own observations, arbitrarily chosen R^0 values will be introduced into the gene analysis, to determine which assumption conforms best with the actual observations.

1st assumption: R^0 lacking.

The sum of the gene frequencies $R^1 + R^2 = 91.6$ per cent; the difference from 100 per cent is 8.4 per cent. We believe that the entire difference represents the frequency of gene R^z, but since only a few Hr tests have been made it could be that the percentage of R^z makes up only part of the difference 8.4 per cent.

2nd assumption: Equal frequencies of R^z and R^0.

According to this assumption the difference, 8.4 per cent, comprises equal percentages of genes R^z and R^0.

If $R^0 = 4.2$ per cent the frequency of type Rh_0 should be very small $(0.042)^2 = 0.18$ per cent, which agrees with the actual observation that not one type Rh_0 individual was found among more than 200 Indians.

The frequencies of genes R^1 and R^2 can then be recalculated as follows:

$$Rh_1 = 0.227 = R^1R^1 + 2R^1R^0,$$
$$R^1R^1 + 2R^1(0.042) + (0.042)^2 = 0.227 + (0.042)^2,$$
$$R^1 + 0.042 = \sqrt{0.227 + 0.002},$$
$$R^1 = \sqrt{0.229} - 0.042 = 43.6\%.$$

Similarly, $R^2 = \sqrt{0.193 + 0.002} - 0.042 = 38.4\%$,

and the sum $R^1 + R^2 + R^0 = 43.6 + 38.4 + 4.2 = 86.2\%$,

which is very low. Correspondingly, the difference from 100 per cent is considerable, namely, 13.8 per cent.

Therefore, the first assumption that $R^0 = 0$, in which the difference is much smaller (only 8.4 per cent), appears more plausible.

3rd assumption: Relatively high R^0 value.

According to the serological findings, the R^0 frequency could also be greater than 4.2 per cent. If, for instance, it were 7 per cent, only one type Rh_0 individual among 200 Indians would be expected. Actually no type Rh_0 individual was found, but this is not necessarily contrary to the assumption $R^0 = 0.07$.

On this assumption we get the following gene frequencies:

$$R^0 = \sqrt{0.005} = 0.071 \text{ or } 7.1\%,$$
$$R^1 = \sqrt{0.227 + 0.005} - 0.071 = 41.1\%,$$
$$R^2 = \sqrt{0.193 + 0.005} - 0.071 = 37.4\%.$$

The sum of the gene frequencies, $R^1 + R^2 + R^0 = 41.1 + 37.4 + 7.1 = 85.6$ per cent. is accordingly still smaller, and the disagreement even greater than under the second assumption.

4th assumption: Small R^0 value.

Assume that $R^0 = 1$ per cent, so that the frequency of type Rh_0 would be very low, 0.01 per cent. The gene distribution would be then as follows:

$$R^0 = \sqrt{.0001} = .01 \text{ or } 1\%,$$
$$R^1 = \sqrt{0.227 + 0.0001} - 0.01 = 46.7\%,$$
$$R^2 = \sqrt{0.193 + 0.0001} - 0.01 = 42.9\%.$$

We see that when even a very small R^0 value is introduced into the calculation, the gene sum $R^1 + R^2 + R^0 = 46.7 + 42.9 + 1.0 = 90.6$ per cent already becomes smaller than under our first assumption.

The following table shows the gene sums and their differences from 100 per cent, resulting from different R^0 values arbitrarily assumed.

	R^0 PERCENTAGES ARBITRARILY ASSUMED			
	0	1	4.2	7.1
Gene sum $R^1 + R^2 + R^0$	91.6	90.6	86.2	85.6
Difference from 100% (= R^2?)	8.4	9.4	13.8	14.4

Even the assumption of a small R^0 value (1 per cent) lowers the gene sum, which decreases continually with increasing R^0 values. The introduction of higher R^2 values to balance the difference from 100 per cent, however, is not a satisfactory solution.

Therefore, the assumption that there is a substantial proportion of gene R^0 in our material becomes improbable, and our observations do not support the crossing-over hypothesis.

TABLE 5. DISTRIBUTION OF THE RH TYPES IN VARIOUS POPULATIONS

POPULATION	INVESTIGATORS	NO. OBS.	rh	rh′	rh″	rh′rh″	Rh₀	Rh₁		Rh₂	$Rh_1Rh_2(Rh_z)$	
								hr′−	hr′+		hr′+	hr′−
Basques	Chalmers, *et al.*, 1948	167	28.7	1.8			0.6	7.8	47.3	7.8	6.0	
Caucasoids												
U. S. A.	Wiener, 1947; Wiener, Sonn, & Polivka, 1946	766	12.5	0.9	0.5		2.2	20.9	33.8	14.9	13.9	0.1
England	Fisher & Race, 1946; Race, Mourant & McFarlane, 1946	927	14.8	0.7	1.3		2.5	19.7	35.2	12.2	13.6	0.1
Brazil	Ottensooser *et al.*, 1948	138	15.2	1.4	0.7		5.8	55.2		10.1	11.6	
Negroids, U. S. A.	Wiener, Belkin, & Sonn, 1944; Wiener, 1945	223	8.1	2.7			41.2	20.2		22.4	5.4	
	Levine, 1945	135	7.4	1.5	0.7		45.9	0.9	22.8	16.3	4.4	
Asiatic Indians	Wiener, Sonn, & Belkin, 1945	156	7.1	2.6			1.9	70.5		5.1	12.8	
Australian aborigines	Simmons & Graydon, 1948	100		1.0			4.0	39.0	14.0	21.0	15.0	6.0
Papuans	Simmons, Graydon, *et al.*, 1946	100						89.0	4.0		4.0	3.0
Filipinos	Simmons & Graydon, 1945	100						87.0		2.0	11.0	
Indonesians	Simmons & Graydon, 1947	200				0.5	0.5	74.0		2.5	22.5	
		(100)						(65)	(9)			
Chinese	Wiener, Sonn, & Yi, 1946	132	1.5				0.9	60.6		3.0	34.1	
Japanese	Miller & Taguchi, 1945	180	0.6					51.7		8.3	39.4	
	Chown *et al.*, 1946	217			0.5			42.8		12.4	43.8	0.5
	Waller & Levine, 1944	150	1.3			0.7		37.4		13.3	47.3	
American Indians												
Mexico	Wiener, Zepeda, *et al.*, 1945	95					1.1	40.7	7.4	9.5	38.1	3.1
U. S. A.	Wiener, Hassler, *et al.*	105		0.9			2.9	34.3	5.7	17.1	36.2	2.9
U. S. A.	Matson & Piper, 1947	104						33.7		28.8	37.5	
Brazil	Present study	238						22.7		19.3	53.2	

TABLE 6. FREQUENCIES OF THE RH GENES IN VARIOUS POPULATIONS

The gene frequencies were calculated by means of the usual formulae (Wiener, Sonn, & Belkin, 1944) except in the following cases:

TABLE 6. FREQUENCIES OF THE RH GENES IN VARIOUS POPULATIONS

The gene frequencies were calculated by means of the usual formulae (Wiener, Sonn, & Belkin, 1944) except in the following cases:

When computing the frequency of the gene R^2 in series where type Rh_2 is scarce (less than 5 percent), the percentage of type Rh_1Rh_2 was used instead of type Rh_2. Similarly, the frequency of gene R^0 in series with very few individuals of type Rh_0 was calculated on the basis of genotype R^1R^0, if tests with anti-hr′ serum showed a relatively high incidence of this genotype.

In most of the series the statistical control was satisfactory with a value of D (difference between sum of the gene frequencies and 100 percent) of less than 2 percent. In three series the value of D reached as high as 6 to 12 percent. One series of table 5 (Australian aborigines) with a still higher difference was excluded from table 6.

POPULATION	NO. OBS.	r	r′	r″	R^0	R^1	R^2	R^z	D
Basques	167	57.2	1.6		0.6	33.8	6.9		+ 0.1
Caucasoids									
U. S. A.	1468	36.5	1.3	0.3	3.2	43.3	14.5		− 0.9
England	927	37.9	0.8	1.7	3.1	43.6	12.8	0.1	0
S. Paulo	138	39.0	1.7	0.9	6.8	40.6	11.5		− 0.5
Negroids, U. S. A.	223	28.5	4.4		41.7	10.4	14.5		− 0.5
	135	27.2	2.6	1.3	45.8	13.0	9.6		− 0.5
Asiatic Indians	156	26.7	4.4		3.3	56.2	11.4		+ 2.0
Papuans	100	(2.1?)			(2.1?)	94.3	2.1	1.5	0
Filipinos	100					93.3	5.9		− 0.8
Indonesians	200				5.6	80.6	14.0		+ 0.2
Chinese	132	12.2			3.3	63.9	26.8		+ 6.2
Japanese	180	7.8				64.5	22.0	(5.7?)	0
	217					65.4	33.5	0.4	− 0.7
	150	11.4				50.8	26.8	(11.0?)	0
American Indians									
Mexico	95				5.8	63.8	26.8	2.4	− 1.2
U. S. A. (Oklahoma)	105		9.5?		17.0?	49.8	27.7	2.4	+ 6.4
U. S. A. (Utah)	104					58.0	53.7?		+11.7
Brazil (Present study)	238					47.6	44.0	8.4	0

DISCUSSION

Data on the distribution of Rh-Hr types in mankind have been compiled only in recent years and are therefore scarce. Among the populations examined there are rather variegated recent mixtures, and one cannot tell to what degree the material selected is representative without consulting the original papers, which are not always accessible. Nevertheless, the combined results of these investigations already have anthropological significance (Levine, 1945; Wiener, 1945; Wiener, 1947; Potter, 1947).

In table 5 our data are compared with those obtained in other countries, especially by Simmons, Graydon, *et al.* in Mongoloids, by Wiener, Zepeda, Sonn and Polivka (1945) in Mexican Indians, and by Wiener, Hassler, *et al.* and by Matson and Piper (1947) in U. S. Indians. Table 6 gives the corresponding gene frequencies for each population.

The Negroid group differs fundamentally from Caucasoids and Mongoloids in the high proportion of gene R^0. The Mongoloid group, on the other hand, is differentiated from Whites and Negroes and also Asiatic Indians by the scarcity or even lack of gene r.

The genes R^1 and R^2 together enable one to distinguish the three major races. The Negroids (Wiener, 1945; Wiener, Belkin & Sonn, 1944; Levine, 1945), have the lowest values of R^1 (less than 15 per cent), the Mongoloids the highest (more than 45 per cent), while the Caucasoids are intermediate (40 to 45 per cent). Some Mongoloids, namely, North American and Brazilian Indians, have relatively low R^1 values approaching those of Whites, but differ sharply from Whites as well as from Asiatic Indians in their high R^2 values.

POPULATIONS	PERCENTAGE OF GENE	
	R^1	R^2
Papuans and Filipinos	More than 90	Less than 10
Indonesians	About 80	About 15
Chinese, Japanese, Mexican Indians, 1 series of U. S. Indians	45–65	20–35
U. S. and Brazilian Indians	45–58	More than 40

Also among themselves, Mongoloid peoples differ in their R^1 and R^2 frequencies. The percentage of other genes being small, there is a roughly reciprocal relationship between the frequencies of genes R^1 and R^2. As a result, the different populations can be arranged according to the frequencies of genes R^1 and R^2, and almost the same order is obtained from the frequencies of the blood types Rh_1 and Rh_2. This is shown in tables 5 and 6, which have been arranged according to this principle.

Summarizing, gene R^1 seems to have its maximum frequencies in Australia and Indonesia, decreasing in the direction of the Asiatic, African and American continents. Gene R^2 behaves inversely. These gradients may be, as in the case of genes *A* and *B* in Eurasia, manifestations of old migrations. The most extreme distributions are especially interesting. The Papuans and Filipinos on one hand have the highest R^1 values and the lowest R^2 values of all the peoples examined; Brazilian and U. S. Indians (Matson & Piper, 1947), on the other hand, have the highest R^2 values and consequently, relatively low R^1 values. There are also American Indians whose R^1 and R^2 frequencies resemble those of Japanese and Chinese.

Even among the American Indians themselves, there occur distinct differences in the distribution of these genes. For example, gene R^1 is more frequent in Mexican than Brazilian Indians, the difference being statistically significant. This is a second variation in the otherwise uniform serological features of American Indians, the other difference consisting of a high percentage of group A in certain U. S. tribes.

The presence of a substantial quota of R^z seems characteristic of American Indians and some other Mongoloid peoples who possess this gene in a frequency 25 to 100 times as high as Whites (Simmons & Graydon, 1947, 1948; Simmons, Graydon, Woods, Smith & Lancaster, 1946; Wiener, 1947; Wiener, Zepeda, Sonn & Polivka, 1945; Wiener, Hassler, *et al.*). This is a positive serological attribute of Mongoloids in contrast to the negative ones, virtual absence of A_2 and Rh-negative individuals.

The particular distribution found in Matto Grosso Indians, with equal R^1 and R^2 frequencies and high proportion of R^z, extends over vast territories. The Caiuá and the Bororo, separated by hundreds of kilometers, have similar frequencies of all the blood types examined. We may therefore assume that our values are representative for certain other Brazilian and Paraguayan tribes also.

SUMMARY AND CONCLUSIONS

Investigations have been carried out on the distribution of the A-B-O groups, M-N types, and Rh types among Caiuá and Bororo Indians in the State of Matto Grosso (Brazil).

All 356 Indians tested (237 Caiuá and 119 Bororo) belonged to group O.

Among 134 Caiuá, 79.9 per cent belonged to type M, 0.7 per cent to type N, and 19.4 per cent to type MN.

Among 173 Caiuá and 103 Bororo, not a single Rh-negative individual was found.

The distribution of the Rh types among 135 Caiuá and 103 Bororo were almost identical. The average frequencies of the types are 22.7 per cent type Rh_1, 19.3 per cent type Rh_2, and 58.0 per cent Rh_1Rh_2. The sum of the gene

frequencies $R^1 + R^2 = 0.476 + 0.440$ is less than 1, and the difference .084 apparently is due to the presence of a third gene, R^z, as can be demonstrated by Hr tests. The findings do not support the crossing-over hypothesis.

American Indians are related to Mongoloids as shown by certain serological findings such as an appreciable frequency of R^z, scarcity or absence of the Rh-negative type, and they are also distinguished by their frequencies of O, M, and Rh_2. Among Matto Grosso Indians these frequencies are especially high.

REFERENCES

BERARDINELLI, W., & ROITER, M. 1934. *Hospital*, Rio. 6: 1129–1135.

BIOCCA, E., & OTTENSOOSER, F. 1944. *Arq. biol.*, S. Paulo, 28: 111–118.

CHALMERS, J. N. M., IKIN, E. W., & MOURANT, A. E. 1948. *Nature*, Lond. 162: 27.

CHOWN, B., OKAMURA, Y., & PETERSON, R. F. 1946. *Canad. J. Res.* 24: 135–143.

ETCHEVERRY, M. A. 1945. *Dia méd.*, B. Air. 17: 1237–1245.

ETCHEVERRY, M. A. 1949. *Hemat. y Hemoter.* 1: 114.

FABRICIUS-HANSEN, V. 1939. *J. Immun.*, Balt. 36: 523–530.

FERNANDES, L. 1939. *Rev. méd. Paraná.* 8: 17–24.

FISHER, R. A. 1947. *Am. Scientist*, 35: 95–102–113.

FISHER, R. A., & RACE, R. R. 1946. *Nature*, Lond. 157: 48–49.

GLASS, B. 1948. *Proc. 8th International Cong. Genetics;* Unpublished.

GRAYDON, J. J., & SIMMONS, R. T. 1945. *Med. J. Australia*, 1: 601–604.

GRAYDON, J. J., & SIMMONS, R. T. 1946. *Med. J. Australia*, 1: 135–138.

GREVAL, S. D. S., & ROYCHOWDHURY, A. B. 1946. *Nature*, Lond. 157: 411.

DAS GUPTA, C. R. 1944. *Ind. M. Gaz.* 77: 372–376.

HENCKEL, K. O., CASTELLI, A., & DAL BORGO, J. 1941. *Bol. Soc. biol. Concepción.* 15: 37–41.

JORDAN, D. 1946. *Canad. M. Ass. J.* 54: 429–434.

KHANOLKAR, V. R., & SANGHVI, L. D. 1945. *Nature*, Lond. 155: 427–428.

LANDSTEINER, K., WIENER, A. S., & MATSON, G. A. 1942. *J. Exp. M.* 76: 73–78.

LEVINE, P. 1945. *Biometr. Bull.* 1: 20–21.

LEVINE, P. 1945. *Nature*, Lond. 156: 418–419.

LEVINE, P., & WONG, H. 1943. *Am. J. Obst.* 45: 832–835.

MATSON, G. A., & PIPER, C. L. 1947. *Am. J. Phys. Anthrop.* 5: 357–368.

MILLER, E. B., & TAGUCHI, T. 1945. 51: *J. Immun.*, Balt. 51: 227–230.

MOLLISON, P. L., & REDDY, D. J. 1946. *Nature*, Lond. 158: 629.

MURRAY, J. 1946. *Nature*, Lond. 158: 306.

OTTENSOOSER, F. 1944. *Rev. brasil. biol.* 4: 531–537.

OTTENSOOSER, F., LACAZ, C. S., FERREIRA, H. C., & MELLONE, O. 1948. *Blood*, Balt. 3: 696–698.

OTTENSOOSER, F., & PASQUALIN, R. 1949. *Arq. biol.*, S. Paulo, 33: 8–18.

OTTENSOOSER, F., & VERSIANI, V. 1949. *Arq. biol.*, S. Paulo, 33: 43–46.

PINKERTON, F. J. 1944. *Hawaii M. J.* 4: 84–85.

POTTER, E. L. 1947. *Rh . . . its relation, etc.* Chicago: Year Book Publishers.

RACE, R. R., MOURANT, A. E., & MCFARLANE, M. N. 1946. *Rev. hémat.*, Par. 1: 9–21.

RANGANATHAN, K. S., RAMACHANDRA RAO, C. S., & RATNAKANNAN, N. R. 1946. *Nature*, Lond. 157: 411.

RIBEIRO, L. 1934. *C. rend. Soc. biol.* 117: 777–778.

SANDOVAL, L., HENCKEL, C., & GIVOVICH, L. 1946. *Blood*, Balt. 1: 555–559.

DA SILVA, E. M. 1948. *Am. J. Phys. Anthrop.* 6: 423–428.

DA SILVA, E. M. In press.
SIMMONS, R. T., GRAYDON, J. J., & OUWEHAND, C. 1945. *M. J. Australia*, 1: 108–110.
SIMMONS, R. T., & GRAYDON, J. J. 1945. *Med. J. Australia*, 2: 325–328.
SIMMONS, R. T., GRAYDON, J. J., & BARNES, G. 1945. *Med. J. Australia*, 1: 529–532.
SIMMONS, R. T., GRAYDON, J. J., WOODS, E. F., HUGH SMITH, W. A., & LANCESTER, H. O. 1946. *M. J. Australia*, 1: 537–539.
SIMMONS, R. T., GRAYDON, J. J., & HAMILTON. 1946. *M. J. Australia*, 1: 553.
SIMMONS, R. T., & GRAYDON, J. J. 1947. *Med. J. Australia*, 1: 577–581.
SIMMONS, R. T., & GRAYDON, J. J. 1948. *Med. J. Australia*, 2: 113–118.
VACCARO, H., STAEDING, J., & GANZARAIN, R. 1948. *Rev. chilena hig.* 10: 121–147.
WALLER, R. K., & LEVINE, P. 1944. *Science*, 100: 453–454.
WIENER, A. S. 1945. *Tr. Coll. Physicians Philadelphia*. 13: 105–122.
WIENER, A. S. 1946. *Science*, 103: 147.
WIENER, A. S. 1947. *This Month in American Medicine*, January 1–12.
WIENER, A. S. 1947. *Advance. Int. Med.*, N. Y. 2: 439–480.
WIENER, A. S. 1949. *Proc. 8th Internat. Cong. Genetics*, *Hereditas*, Suppl. Vol., 500–519.
WIENER, A. S., BELKIN, R. B., & SONN, E. B. 1944. *Am. J. Phys. Anthrop.* 2: 187–194.
WIENER, A. S., HASSLER, F. R., SONN, E. B., & POLIVKA, H. R. Unpublished data.
WIENER, A. S., SONN, E. B., & YI, C. L. 1944. *Am. J. Phys. Anthrop.* 2: 267–273.
WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1944. *J. Exp. M.* 97: 235–253.
WIENER, A. S., SONN, E. B., & BELKIN, R. B. 1945. *J. Immun.*, Balt. 50: 341–348.
WIENER, A. S., SONN, E. B., & POLIVKA, H. R. 1946. *Proc. Soc. Exp. Biol.*, N. Y. 61: 382–390.
WIENER, A. S., ZEPEDA, J. P., SONN, E. B. & POLIVKA, H. R. 1945. *J. Exp. M.* 81: 559–571.

The Incidence of Consanguineous Matings in Japan

With Remarks on the Estimation of Comparative Gene Frequencies and the Expected Rate of Appearance of Induced Recessive Mutations[1]

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THE frequency of occurrence of consanguineous marriages has been rather extensively investigated in European populations. There exist, however, relatively few exact data for other parts of the world. The following studies were undertaken in an attempt to supply information on this point for one type of Mongolian population, namely, Japanese residing on the islands of Honshu and Kyushu.

Investigations of this type were formerly of interest primarily to the social anthropologist. More recently, students of human genetics have realized the significance of this information for the solution of certain of their problems. The authors have been particularly interested in the light such data might throw on two questions, namely, 1) the rate with which any recessive mutations induced by the atomic bombings of Hiroshima and Nagasaki might be expected to appear in the descendants of the survivors, and 2) the comparative frequencies of certain inherited traits in Caucasian (European) and Mongolian (Japanese) populations.

THE DATA

The data which we have collected on the incidence of consanguinity in Japan fall into two different categories.

A. Pregnancy Registration Results

During the period covered by this investigation (1948–1949), a system of voluntary pregnancy registration was in force throughout Japan. As soon as the fifth month had been reached, a pregnant woman was entitled upon registration to receive certain rationed items. Because of the economic stringencies obtaining in Japan during this period, registration was relatively complete. In connection with an attempt to investigate the potential genetic ef-

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fects of the atomic bomb, there has been superimposed upon this system of pregnancy registration a special questionnaire in Hiroshima and Nagasaki, and in a control city, Kure. This special questionnaire includes an item concerning consanguinity. In point of size, these towns are respectively the fifteenth, nineteenth, and twenty-second largest in Japan, having on the basis of the 1947 census populations of 224,100, 198,642, and 185,740, and the results secured in these localities may be regarded as more or less typical of the cities of southern Japan. All registration clerks have been carefully schooled concerning the various degrees of consanguinity and the manner in which to elicit information on this point. Thus far a total of 23,804 questionnaires have been completed. The results are given in table 1. Of the women registering, 93.5 per cent were between the ages of 20 and 39; these results therefore tend to reflect the situation with respect to marriages contracted between 1929 and 1948.

In connection with the above-mentioned genetic studies, it has been customary, upon the report of the termination of certain of these pregnancies, to make a follow-up visit to the home of the woman in question. On the occasion of that visit, the question of consan-

TABLE 1. THE FREQUENCY OF CONSAGUINEOUS MARRIAGE AMONG WOMEN REGISTERING AS PREGNANT IN THREE JAPANESE CITIES DURING 1948 AND 1949

CITY AND POPULATION (1947 Census)	NUMBER OF WOMEN REGISTERED	FIRST COUSIN	FIRST COUSIN ONCE REMOVED	SECOND COUSIN	OTHER CONSAN-GUINITY	TOTAL CONSAN-GUINITY
Hiroshima 224,100	10,547	391 (3.71%)	101 (0.96%)	164 (1.56%)	28 (0.27%)	684 (6.49%)
Kure 185,740	5,510	226 (4.10%)	79 (1.43%)	109 (1.98%)	17 (0.31%)	431 (7.82%)
Nagasaki 198,642	7,747	406 (5.24%)	87 (1.12%)	153 (1.98%)	12 (0.15%)	658 (8.49%)
Total.....	23,804	1,023 (4.30%)	267 (1.12%)	426 (1.79%)	57 (0.24%)	1,773 (7.45%)

guinity was again raised; the interviewer was not aware of the nature of the previous statement. Out of a total of 1,681 women so interviewed, 22 failed to confirm their previous statements concerning consanguinity, or stated a degree of relationship other than that previously obtained. This is a significant discrepancy. No particular trend was evident, i. e., in eight instances women who had previously stated that consanguinity existed now admitted to no such relationship, in six cases the reverse was true, while in eight other cases the degree of relationship was otherwise than originally stated. To what extent the second statement represents the result of further inquiry into the matter and hence is more accurate, is not clear. If we assume that all women who have on either of the two occasions stated that theirs was a consanguineous marriage are, in fact, related to their husbands, then the overall incidence of consanguinity would be about 0.36 % higher.

B. Special Survey Results

The consanguinity data obtained from the genetic questionnaires were of such interest that several special surveys were undertaken in an attempt to secure a more rounded picture of the situation. A sector of Hiroshima (the Hijiyama district) was selected as more or less

typical of the city as a whole, and an attempt was made to obtain a statement from each married couple in that sector concerning consanguinity. A similar procedure was carried out in Kure (the Katayama district). This procedure yielded a wider age distribution than the previous study, making possible an analysis of the data for secular trends. In addition, two special areas located near Kure were studied. The first of these (Midori Machi) is situated on the outskirts of Kure and was of special interest because it is an Eta village. For centuries those persons in Japan who work with the flesh or its products (e. g., butchers, leather workers) have tended to be isolated socially from the rest of the population, corresponding in a sense to India's untouchables. These persons are known as Etas. They have aggregated into special villages or sections of the larger towns. It was the impression of the Japanese Nationals with whom we talked in the planning of this investigation that the incidence of consanguinity was especially high in such communities. The second area selected for special

TABLE 2. SUMMARY TABLE OF FREQUENCIES OF VARIOUS CONSANGUINEOUS MARRIAGES IN DIFFERENT KINDS OF POPULATION IN KURE AND HIROSHIMA, HIROSHIMA PREFECTURE, HONSHU, JAPAN

LOCALITY	NUMBER OF MARRIED COUPLES	FIRST COUSIN	FIRST COUSIN ONCE REMOVED	SECOND COUSIN	SECOND COUSIN ONCE REMOVED	THIRD COUSIN	THIRD COUSIN ONCE REMOVED	TOTAL NUMBER AND PERCENTAGES OF ALL CONSANGUINEOUS MARRIAGES	IN-LAW MARRIAGES
Hiroshima (city)	3283	129 (3.93%)	38 (1.16%)	69 (2.10%)	18 (0.55%)	6 (0.18%)	1 (0.03%)	261 (7.95%)	76 (2.39%)
Kure (city)	1642	98 (4.64%)	31 (1.47%)	40 (1.89%)	5 (0.24%)	2 (0.09%)	0 (0.0%)	176 (8.33%)	70 (3.36%)
Midori Machi (Eta village)	147	8 (5.44%)	3 (2.72%)	2 (1.36%)	0 (0.0%)	1 (0.61%)	0 (0.0%)	14 (10.13%)	10 (1.47%)
Dainu (village)	323	23 (7.12%)	6 (1.86%)	7 (2.17%)	1 (0.31%)	0 (0.0%)	0 (0.0%)	37 (11.46%)	9 (2.79%)
Total.....	5395	258 (4.78%)	78 (1.45%)	118 (2.19%)	24 (0.44%)	9 (0.17%)	1 (0.02%)	488 (9.05%)	115 (2.13%)

study was a fishing community (Dainu) located some six miles from Kure, with a population of 1,787. Except for its proximity to a large city, this settlement may be regarded as more or less typical of the smaller agricultural and fishing villages of southern Honshu, the main island of Japan.

The results are shown in tables 2 and 3. Minor discrepancies in percentages and totals between the two tables are related to the inability to obtain accurate ages in some cases where a spouse was deceased or divorced, and the consequent necessity of omitting some persons from table 3 who are represented in table 2. The rate of consanguinity observed in Kure and Hiroshima by this approach (table 2) agrees well with that seen in the previous study. Consanguinity rates appear to be higher in the smaller communities, although because of the numbers involved the differences are not significant. It is noteworthy that the consanguinity rates in the Eta village under consideration were not higher than those of a fishing village of somewhat larger size. In all four of the communities studied the affinity rate,

as measured by the frequency of "in-law" marriages, is quite high. This is an understandable corollary of a high consanguinity rate. Table 3 reveals no significant tendency for consanguinity rates to have altered in the past sixty years, although first cousin marriages may have been somewhat more common among the older individuals.

The two smaller communities studied were actually relatively accessible. The question naturally arose as to what the consanguinity rates might be in some of the smaller but less accessible coastal and interior villages. At our suggestion, Dr. F. Kida and associates of Kumamoto University undertook a rather extensive survey of some of the towns and villages of the island of Kyushu, Japan. Their results, which have been reported elsewhere (Kida, Kanokogi, and Kojima, 1949), are shown in table 4. The communities investigated

TABLE 3. THE SECULAR TREND WITH RESPECT TO CONSANGUINEOUS MARRIAGES IN THE FOUR AREAS STUDIED

a. As related to age of male partner

DEGREE OF CONSANGUINITY	MALE AGE GROUP			
	21–40 yrs.	41–60 yrs.	61–80 yrs.	Total
First cousin	94 (4.24%)	87 (4.08%)	26 (4.73%)	207 (4.23%)
First cousin once removed	36 (1.62%)	21 (0.99%)	6 (1.09%)	63 (1.29%)
Second cousin	65 (2.93%)	31 (1.45%)	11 (2.00%)	107 (2.18%)
Total marriages	2217	2131	550	4898

b. As related to age of female partner

DEGREE OF CONSANGUINITY	FEMALE AGE GROUP			
	17–40 yrs.	41–60 yrs.	61–80 yrs.	Total
First cousin	122 (4.07%)	68 (5.03%)	18 (5.90%)	208 (4.47%)
First cousin once removed	42 (1.40%)	25 (1.85%)	1 (0.33%)	68 (1.46%)
Second cousin	76 (2.53%)	20 (1.48%)	7 (2.30%)	103 (2.21%)
Total marriages	2999	1353	305	4657

have been classified as cities (only one: Kumamoto city, population 245,841), towns (population 6,981 to 13,149), and villages (population 1,818 to 4,352). The consanguinity rates encountered in some of these villages are as high as any we have found recorded in the literature.

THE UTILIZATION OF THESE DATA IN VARIOUS CALCULATIONS

The magnitude of the consanguinity rates encountered in this study may best be appreciated by reference to table 5, which summarizes the findings with respect to consanguinity in a number of European populations. Although certain isolated European communities exhibit rates comparable to those encountered in Japan, there has to date been recorded no major population or

geographical unit with rates of this magnitude. The combining of the Kure and Hiroshima data on consanguinity into a single figure may be accomplished through the use of Wright's *coefficient of inbreeding*, α. For the most extensive

TABLE 4. SUMMARY OF THE FREQUENCY OF VARIOUS DEGREES OF CONSANGUINEOUS MARRIAGE IN DIFFERENT TYPES OF POPULATION UNITS IN KUMAMOTO PREFECTURE, KYUSHU, JAPAN (DATA OF KIDA, KANOKOGI, AND KOJIMA, 1949)

LOCALITY	NUMBER OF MARRIED COUPLES	FIRST COUSIN	FIRST COUSIN ONCE REMOVED	SECOND COUSIN	SECON COUSIN ONCE REMOVED	OTHER CONSANGUINEOUS MARRIAGES	SEEM TO BE CONSANGUINEOUS BUT UNCERTAIN	TOTAL (EXCLUDING UNCERTAIN CASES)
Kumamoto City (city)	1830	63 3.4%	31 1.6%	23 1.2%	6 0.3%	0 0.0%	6 0.3%	124 6.7%
Yamashika (town)	2902	162 5.5%	42 1.4%	46 1.5%	19 0.6%	3 0.1%	4 0.1%	276 9.5%
Waifu (town)	2908	175 6.2%	48 1.6%	52 1.7%	16 0.5%	3 0.1%	12 0.4%	298 10.2%
Udo (town)	1092	56 5.1%	15 1.4%	26 2.4%	3 0.2%	2 0.1%	4 0.3%	103 9.4%
Toride (village)	459	39 8.5%	13 2.8%	12 2.6%	1 0.2%	2 0.4%	0 0.0%	68 14.8%
Hanabusa (village)	390	33 8.5%	6 1.5%	10 2.5%	3 0.7%	0 0.0%	0 0.0%	52 13.3%
Kikuchi (village)	888	84 9.4%	14 1.5%	26 2.9%	11 1.2%	0 0.0%	4 0.4%	142 15.9%
Asahino (village)	416	28 6.7%	15 3.6%	12 2.8%	3 0.7%	1 0.2%	3 0.7%	59 14.1%
Suigen (village)	776	96 12.4%	29 3.7%	15 1.9%	11 1.4%	1 0.1%	2 0.2%	152 19.5%
Higashi Nagashima (village)	1788	204 11.4%	45 2.5%	57 3.1%	26 1.4%	1 0.1%	24 1.3%	336 18.7%
Nishi Nagashima (village)	1433	205 14.3%	38 2.6%	55 3.8%	18 1.2%	2 0.1%	13 0.9%	320 22.3%

European data available, those of Orel (1932) on the archdiocese of Vienna, the observed α approximates 0.00060 (Haldane & Moshinsky, 1939). For our Japanese data on urban populations, the observed α in women registering pregnancies for ration purposes approximates 0.00372. Both figures are of course underestimates, since some individuals are doubtless unaware of even relatively

recent and close consanguinity, and, further, because of the relatively rapid expansion of the world's population, remote consanguinity must be involved in

TABLE 5. THE INCIDENCE OF CONSANGUINITY IN VARIOUS TYPES OF EUROPEAN POPULATION GROUPS
For the purpose of convenience, the material has somewhat arbitrarily been classified into "normal populations" and "isolates"

MATERIAL AND AUTHOR	PERIOD	FREQUENCY OF FIRST COUSIN MARRIAGES	FREQUENCY OF CONSANGUINEOUS MARRIAGES UP TO AND INCLUDING SECOND COUSINS
a. "Normal Populations"			
Europe. World literature, plus assumptions as to number of consanguineous marriages not so stated. (Lenz, 1919)	±1875–1910	1.0%	2.6%
Germany. 453 Catholic and Protestant marriages in 3 villages in rural Württemberg. (Spindler, 1922)	±1875–1920	1.8 ± 0.7	9.6 ± 1.4
Germany. 5,283 marriages in 40 Bavarian parishes—predominantly a rural Catholic population. (Wulz, 1925)	1848–1872	0.49 ± 0.096	1.07 ± 0.14
Germany. 5,706 marriages in 40 Bavarian parishes—predominantly a rural Catholic population. (Wulz, 1925)	1873–1897	0.65 ± 0.11	1.33 ± 0.15
Germany. 5,193 marriages in 40 Bavarian parishes—predominantly a rural Catholic population. (Wulz, 1925)	1898–1922	0.67 ± 0.11	1.52 ± 0.17
Austria. 40,697 Catholic marriages in Vienna and environs. (Orel, 1932)	1901–1902	0.77 ± 0.043	1.12 ± 0.052
Austria. 44,911 Catholic marriages in Vienna and environs. (Orel, 1932)	1913–1914	0.68 ± 0.039	1.24 ± 0.052
Austria. 31,823 Catholic marriages in Vienna and environs. (Orel, 1932)	1929–1930	0.53 ± 0.041	0.99 ± 0.056
Prussia. 1,286,339 marriages	1875–1880	0.71 ± 0.0074	
Prussia. 2,122,300 marriages	1921–1926	0.20 ± 0.0033	
Bavaria. 188,973 marriages	1876–1880	0.87 ± 0.021	
Bavaria. 474,268 marriages	1926–1933	0.20 ± 0.0066	
France. 1,410,889 marriages	1876–1880	1.03 ± 0.0085	
France. 1,350,683 marriages (Dahlberg, 1939)	1914–1919	0.97 ± 0.0085	
England. Parents of 49,315 adult in-patients of general hospitals. (Bell, 1940)	±1880–1925	0.61 ± 0.035	
England. Parents of 10,236 child in-patients of general hospitals (Bell, 1940)	±1925–1939	0.40 ± 0.062	
Denmark. Parents of 498 randomly selected young propositi in Copenhagen. (Bartels, 1941)	±1900–1920	1.2 ± 0.5	

TABLE 5.—*Continued*

MATERIAL AND AUTHOR	PERIOD	FREQUENCY OF FIRST COUSIN MARRIAGES	FREQUENCY OF CONSANGUINEOUS MARRIAGES UP TO AND INCLUDING SECOND COUSINS
b. "Isolates"			
Fiji Islands. 448 marriages in 12 villages where local custom encouraged cousin marriages. (Pearson, 1911)	±1850–1895	29.7 ± 2.2%	
Germany. 117 marriages among Hohenzollern Jews. (Reutlinger, 1922)	±1875–1920	16.2 ± 3.4	19.6 ± 3.7%
Switzerland. 270 marriages in an Alpine community. (Brenk, 1931)	±1870–1923	1.9 ± 0.8	9.7 ± 1.8
Germany. 380 marriages in an isolated Protestant community of the Rhineland. (auf der Nöllenburg, 1932)	1840–1889	5.3 ± 1.2	11.1 ± 1.6
Switzerland. 52 marriages in Obermatt. (Egenter, 1934)	±1890–1932	11.5 ± 4.4	53.8 ± 6.9
Switzerland. 139 marriages in an Alpine community. (Grob, 1934)	±1885–1932	0.7 ± 0.7	9.9 ± 2.5
Switzerland. 77 marriages in an Alpine community. (Ruepp, 1935)	±1880–1933	3.9 ± 2.2	19.5 ± 4.5
Sweden. Parents of 332 randomly selected persons on a small, rural Swedish island. (Sjögren, 1948)	±1850–1920	3.0 ± 0.9	
Sweden. All marriages in the populations of three northern parishes:	±1880–1945		
Pajola (population of 5943)		1.0 ± 0.3	
Junosuando (population of 1871)		2.9 ± 1.0	
Muonionalusta (population of 1376) (Böök, 1948)		6.8 ± 1.8	

a sizeable fraction of marriages. Taken at face value, however, these figures indicate a degree of inbreeding in the Japanese which is about six times that observed in a roughly comparable European population. In the European data, 72% of the known value of α was contributed by first cousin marriages; in the Japanese data, 78% of the known value is due to marriages of this type.

Two general groups of factors operate in the production of high consanguinity rates, namely, geographical and social, including in the latter category both localized social pressures and social customs. Factors of the former type are primarily responsible for the findings of Nöllenburg (1932), Egenter (1934), and

Böök (1948) with respect to small and isolated German, Swiss, and Swedish communities, while factors of the latter type account for the consanguinity rates sometimes observed among members of Jewish groups (Reutlinger, 1923) or the Fiji Islanders (Pearson, 1911). It seems probable that in Japan both these types of factors are at work. Although Japan is a small and heavily populated country, it is our impression that there is a considerable degree of relative isolation between its various villages, especially those in the interior, with—at least prior to the disruptions of the war—a less mobile population than is true of many other countries. A more important contributing factor than this is to be found in the social structure of the country. There is, to begin with, a relatively rigid stratification, with, for the most part, opportunities for marriage only within one's stratum. On top of this, marriage in Japan is still guided to a great extent by parental wishes. Parents, wishing to conserve the family assets, and being reluctant to underwrite the risks involved in the selection of a marriage partner whose quality is relatively unknown, will understandably often choose from within the family circle.

Dahlberg (1948) has presented formulae for calculating the size of the "isolates" into which a population is subdivided on the basis of the frequency of cousin marriages. Such formulae assume that cousin marriages are contracted at random. While possibly of value in certain European countries, the formulae would have a more limited usefulness as applied to Japan, since here the group within which any individual might contract a marriage might be divided into two fractions, one composed of relatives, with whom the probability of marriage is disproportionately high, and one composed of nonrelatives, with whom the probability of marriage is somewhat lower.

The Estimation of Gene Frequencies

A genetically satisfactory evaluation of anthropological differences is possible only in terms of the relative frequencies of specific genes and their interaction with local environmental factors. Thus far, this type of evaluation has been feasible only for certain rather common genes of comparatively little adaptive significance, such as those responsible for the A-B-O blood groups and M-N types, color-blindness, and the ability to taste phenylthiocarbamide (review in Snyder, 1947). A further step would consist in a comparison of the frequency of various recessive traits with a considerable selective disadvantage. Direct surveys of the necessary magnitude have not yet been carried out. However, there is an indirect approach to the problem. The frequency of a given recessive gene may be calculated if the incidence of first cousin marriages in the general population and among the parents of affected individuals is known, and if one assumes panmixia. Formulae suitable for this calculation have been proposed by Lenz (1919), Weinberg (1920), Dahlberg (1938, 1948), and Hogben

(1946), among others; these all yield approximately the same result but that proposed by Weinberg and Dahlberg is perhaps preferable, namely,

$$k = \frac{c}{c + \frac{16(1-c)q}{1+15q}},$$

or, restated in terms of q,

$$q = \frac{c(1-k)}{16k - 15c - ck},$$

where q = the frequency of the recessive gene responsible for the trait in question,

k = the proportion of first cousin marriages among the parents of affected persons, and

c = the proportion of first cousin marriages among the population as a whole.

The relationships of q, c, and k are graphically illustrated in figure 1. As we shall see below, figure 1 allows for an estimation of gene frequencies which is certainly as accurate as the data justify.

The use of this formula is subject to very severe limitations, some of which have been clearly stated in the past and some of which have not. Dahlberg (1938, 1948) has pointed out in particular the theoretical pitfalls inherent in the use of this equation. Human populations of any magnitude are not in a state of panmixia, but are broken up into isolates of greater or lesser degree between which there occur significant variations in gene frequency. In the case of Japan, and possibly for other countries either now or in the past, the isolate effect is intensified by a tendency for the mating of related persons within the isolate—i.e., the definition of isolate size is complicated by local custom.

Although it is clear that the occurrence of these isolates may in specific instances invalidate the use of this formula where extreme accuracy is desired, it is not yet apparent to what extent the formula may be relied on for a serviceable approximation to gene frequencies. It is certain that the concept of complete isolates is as spurious as the concept of panmixia; over a period of years there is a very substantial gene exchange between neighboring communities. However, at the present time the coefficients of migration and interchange cannot even be approximated for the sub-groups comprising any sizeable human population. Accordingly, while there can be no doubt of the theoretical importance of isolates, there is no human population whose breeding structure is sufficiently well known to enable us to estimate the inaccuracies introduced by isolate effects. In the present case, we are not so much interested in absolute values as in comparative values; the formula may have greater validity in this latter context. This question, of the appropriateness of using

the equation given above for a first approach to the problem, will be returned to after we have considered the biological shortcomings of the data.

In addition to purely theoretical pitfalls, there are many biological complications standing in the way of the estimation of gene frequencies. The traits

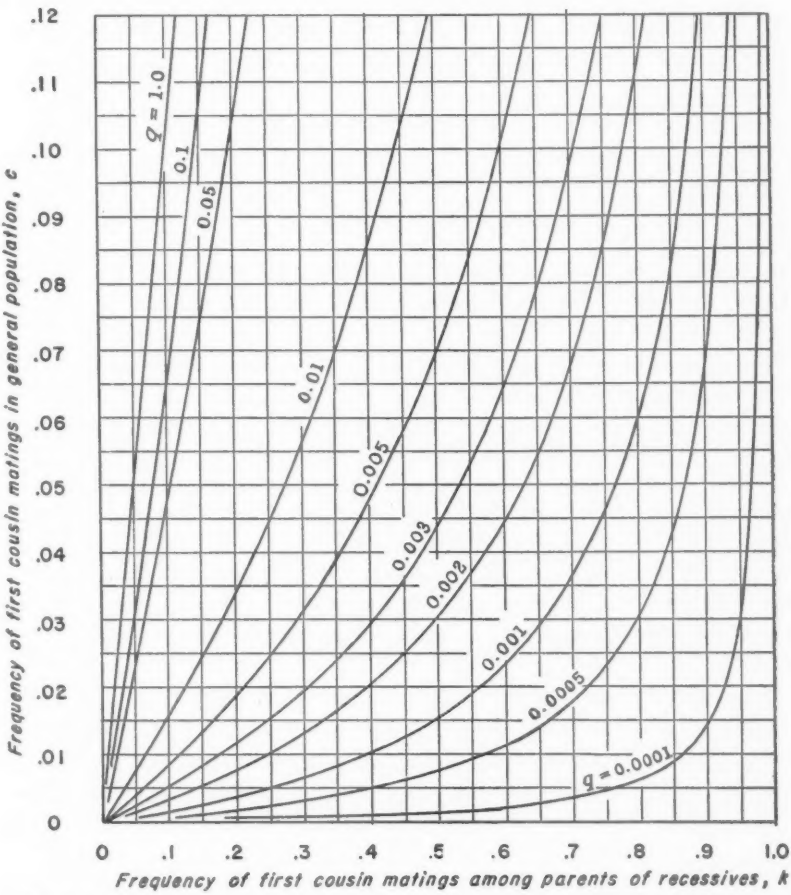

FIG. 1. Recessive gene frequency (q) as a function of the frequency of first cousin mating among the general population (c) and among the parents of recessives (k). $q = c(1 - k)/(16k - 15c - ck)$.

selected for consideration must always be clearly differentiated from normal, and must satisfy all the criteria for monogenic recessive inheritance. It will never be possible to be certain in man that a given recessive trait is always due to the same recessive gene. Gates (1946) has cited numerous illustrations where what to the clinician appears to be one and the same condition may have

different genetic bases in different families. Thus, retinitis pigmentosa may apparently be due to an autosomal dominant or recessive or a sex-linked dominant or recessive; partial sex linkage also seems to have been established. No matter how carefully one selects diseases for consideration one can never be certain that all cases have the same genetic basis. Furthermore, the estimation of consanguinity in the parentage of any given group of people is subject to very serious errors, both on the part of the recorder and of the persons concerned.

Despite all these well-recognized theoretical and biological factors tending to impair the accuracy of the results obtained with the equation given above, it is of interest, now that data are available concerning the incidence of consanguinity in the Japanese, to inquire into the incidence of consanguinity among the parentage of individuals with certain well-defined recessive traits, and to compare the data so obtained with what is known concerning European populations. Although such an attempt has only limited validity in the light of our present information, quite aside from the tentative conclusions which may be drawn it serves an added purpose in highlighting present gaps in our knowledge of the genetics of man. Table 6 presents data concerning the comparative frequencies of five genes as calculated by this method. In the preparation of this table we have been greatly aided by Dr. R. Kawakami of the Japanese Institute of Public Health, who in the course of assembling a monograph on the genetics of the Japanese has summarized a vast amount of literature not usually available to the Occident, and has kindly made certain of his results available to us in advance of publication, and in particular where there are one or two outstanding studies on which reliance can be placed, made these known to us. We have also used, for purposes of comparison, Komai's two summaries (1934, 1947).

As will be apparent below, the data on the incidence of consanguinity among the parentage of individuals with various recessive traits is quite unsatisfactory. In the table there is indicated a range within which the true value of k may lie. This range is obtained in the following manner. For each trait, a minimum and maximum k value can usually be estimated from the literature. The "true" value lies someplace between these two; for each trait an attempt has been made to estimate this true value. A standard error has then been calculated, using as n the total number of segregating sibships reported. Actually, of course, the range of error involved is greater than that given by the standard error, but for present purposes this error is a sufficient approximation. In these calculations, the c value assumed for the European population is 0.01, and for the Japanese, 0.06. The value of 0.01 is of course too high for contemporary European populations, but probably approximates the true value 40 to 60 years ago, when the parents of many of the sibships on which the calculations are based were married. Although the observed incidence of first cousin marriage

in our two studies of Japanese material was 4.30% and 4.78%, these studies were very heavily weighted in favor of urban-contracted marriages. When allowance is made for this fact and for a possible secular trend, an estimate of 6.0% seems not unreasonable. In selecting for purposes of calculation values of 0.01 and 0.06 we have been perhaps unduly influenced by the findings in urban populations, but feel that in both Europe and Japan these groups prob-

TABLE 6. THE INCIDENCE OF CONSANGUINITY IN THE PARENTAGE OF INDIVIDUALS WITH CERTAIN RECESSIVELY-INHERITED DISEASES, AND THE GENE FREQUENCIES WHICH MAY BE CALCULATED THEREFROM

Comparison of Caucasian (predominantly European) and Japanese figures. (Further explanation in text.)

TRAIT	INCIDENCE OF FIRST COUSIN MARRIAGES AMONG PARENTS (k)	AUTHORITY	RECESSIVE GENE FREQUENCY (q)
1. Albinism			
Caucasian	0.18–0.24	Pearson, 1913	0.0021–0.0030
Japanese	*0.37–0.59*	Kurasima, 1937	*0.0029–0.0075*
2. Infantile amaurotic idiocy			
Caucasian	0.27–0.53	Slome, 1933	0.0006–0.0018
Japanese	*0.55–0.85*	Katsunuma, *et al.*	*0.0007–0.0034*
3. Ichthyosis congenita			
Caucasian	0.30–0.40	Cockayne, 1933	0.0010–0.0015
Japanese	*0.67–0.93*	Yamamoto and Ishikawa, 1939	*0.0003–0.0022*
4. Congenital total color-blindness			
Caucasian	0.11–0.21	Peter, 1926; Bell, 1933; Göthlin, 1941	0.0025–0.0055
Japanese	*0.39–0.51*	Hohki; Hitomi, 1943	*0.0041–0.0069*
5. Xeroderma pigmentosum			
Caucasian	0.20–0.26	Siemens & Kohn, 1925; Cockayne, 1933; Macklin, 1936	0.0019–0.0026
Japanese	*0.37–0.43*	Kawakami	*0.0057–0.0075*

ably contribute disproportionately to persons seen in large medical centers. The assumption of c values somewhat above or below 0.01 and 0.06 would of course quite significantly influence the estimate of q, a fact readily apparent from a consideration of figure 1.

A brief discussion of each of the traits listed in the table follows:

1. **Complete Albinism.** This clear-cut and striking trait has been the object of extensive genetical studies. The evidence for the similarity of the genetic basis of complete albinism in

all cases has been summarized by Cockayne (1933). The data, though scanty, suggest that the great majority of pedigrees of complete albinism depend on one and the same autosomal recessive gene. Although sex-linked complete albinism may exist, it must be very rare. This conclusion has the support of the results of extensive work with albino mammals of several species; only a single gene for complete albinism is recognized in the mouse, rat, guinea-pig, and rabbit, four mammals which have been particularly studied in this respect.

The most extensive work on albinism in man is Pearson's monumental monograph (1913). Dahlberg (1938) states that the incidence of first cousin marriages among the parents of this material is 0.17. Hogben (1946), without stating the source, repeats a similar figure for consanguinity in the parentage of albinos. We have retabulated the data for all albinos recorded as of European parentage, excluding Jews, the latter because of possible genetic differences from other Europeans, and obtain, for 217 families, a figure of 0.21. In this tabulation, quite a number of European families were excluded from consideration because it was felt they had been insufficiently investigated in respect to consanguinity. The adoption of more liberal standards would of course lower the figure given above. The corresponding q value is 0.002–0.003. The most extensive and reliable Japanese study of albinism is that of Kurasima (1937). This investigator personally interviewed the parents of 21 sibships in which albinism had occurred, finding that 10 pairs were first cousins. In the Japanese material on albinism summarized by Komai (1934, 1947), the incidence of parental consanguinity of all types is only 43.7%. The discrepancy is probably a reflection of incomplete ascertainment, and we shall use Kurasima's figures. The corresponding gene frequency is 0.0029–0.0075.

Albinism is sufficiently common and striking that numerous attempts have been made to estimate its frequency. Its incidence in Europeans has been variously placed at from 1:10,000 in Norway to 1:100,000 in Russia (cf. Pearson, 1913, for an extensive review). No one who has considered the basis for these estimates can help but be highly dissatisfied with the available figures and the validity of the alleged differences between various groups. Probably the figure adopted by Hogben (1946), of 1:20,000 for European communities, is as satisfactory as any. Assuming that in the population studied the mean coefficient of inbreeding, α (discussed below), had a value of 0.001, this corresponds to a gene frequency of 0.0066. Kurasima's survey of Gifu prefecture revealed, for the summed population in the years 1901–1935, a total of 559 albinos in 26,685,028 persons, an approximate incidence of 1:47,000. Assuming an α value of 0.005, this corresponds to a gene frequency of 0.0028. This latter figure is in satisfactory correspondence with the Japanese value as calculated by c and k, whereas for the European figures there is a marked discrepancy. This discrepancy has been pointed out by Roberts (1932), Hogben (1946), and Gates (1946), among others, and the suggestion made that it can be explained by the existence of several different genes for albinism. An alternative explanation stems from the fact that many of the pedigrees of albinism in the literature and on which the estimate of $k = 0.21$ is based were collected during the nineteenth or early twentieth century, at which time the value of α may have been sensibly higher than the previously assumed value, approximating 0.002, with $c = 0.02$. Under these circumstances q as calculated from figure 1 would equal 0.005, while as calculated from α and an incidence of 1:20,000 it would equal 0.006. This would appear to constitute a satisfactory agreement, but would tend to throw the European figures somewhat out of line with the Japanese estimate as based on direct methods. It is possible that this latter estimate suffers from a lack of complete ascertainment—a real problem in Japan.

2. **Infantile amaurotic idiocy.** The question of whether the infantile and juvenile forms of amaurotic idiocy have different genetic bases or are due to the same recessive gene, whose mode of expression is very significantly altered by various modifiers, is relatively immaterial in a consideration of gene frequencies, since by treating them as separate and distinct entities

we are merely effecting two estimates of the frequency of the same gene. The apparently greater incidence of amaurotic idiocy among Jews than among Gentiles is well known. Because of possible genetic differences between the two groups, as well as differences in the value of α, we have, as for albinism, restricted our consideration to Gentiles. Unfortunately, this very drastically reduces the amount of material available. Slome in 1933 tabulated 18 sibships in which amaurotic idiocy had appeared in Gentile families. In three of these consanguinity had not been ascertained. The incidence of first cousin marriage in the parentage of the remaining 15 sibships was 0.40. Among 109 Jewish sibships, consanguinity had not been ascertained in 28, with 0.16 first cousin marriages in the remainder. This would appear to point to a valid genetic difference between the two groups, especially in view of the probably higher c value for Jewish groups. The Japanese material is also quite limited. Komai's 1934 summary does not distinguish as to type of amaurotic idiocy; in the 1947 material 3 of 6 sibships segregating for infantile amaurotic idiocy are shown as the results of consanguineous matings. Katsunuma, Murakami, and Takesita in an unpublished manuscript have summarized the Japanese data available to them. They were able to find reports of only 12 sibships in which the disease had appeared, for two of which parental consanguinity had not been ascertained. In the remaining 10 families, the affected children were the offspring of first cousins in seven cases. There is satisfactory agreement between the gene frequency estimates in the two populations as shown in table 6.

The estimates of the incidence of consanguinity among the parents are for European populations much better for the juvenile form of amaurotic idiocy than for the infantile type discussed above (Sjögren, 1931). Unfortunately, the Japanese material on juvenile amaurotic idiocy is so extremely deficient at present as to render a comparison meaningless, Katsunuma, Murakami, and Takesita being able to find reports of only four segregating sibships, two of them the result of first cousin marriages. Sjögren (1931) in his studies on a Swedish population calculated from the k value of 0.15 observed in his material, assuming a c value of 0.01, that the gene frequency was 0.0038. In an independent calculation, based on an observed frequency of infantile amaurotic idiocy of 0.000038 in Sweden, he calculated a gene frequency of 0.0062, and a corresponding frequency of the heterozygotes of 0.012. The agreement between the two approaches appeared satisfactory. He emphasized the sources of error in his calculations and the tentative nature of his conclusions, pointing out the role of isolates (Heterozygotenherde). Dahlberg (1938) has criticized these calculations severely, writing:

"A correct calculation should show that in the isolates where the gene occurs the frequency of heterozygotes is much higher than 1 per cent., whereas the number of heterozygotes as related to the entire population amounts to only a small fraction of 1 per cent."

It is unfortunate that in this rather knotty situation Dahlberg did not publish figures to support his argument. This problem has more recently been approached by Dunn (1947). Using a formula which amounts to an approximation to the one given above,

$$k = \frac{c\,(1 + 15r)}{16r}$$

he first assumed panmixia with a c value of 0.01 and then calculated from Sjögren's data an overall gene frequency of 0.0044. Pointing out (as had Sjögren) the fact that the disease in Sweden tended to occur in localized areas where the effective c value during the period in question ($\pm$1875–1930) more probably approximated 0.02, he then calculated a gene frequency in these of 0.009524. The observed frequency of occurrence (about 4 per 100,000 births) could then be explained if it was assumed that about 40% of the population was

grouped into aggregates with the above gene frequency, while in the remainder the gene frequency was close to zero. However, even if this is the case, the overall gene frequency in the population would approximate $(0.4 \times 0.009524) + (0.6 \times 0.0) = 0.0038$, i. e., a value which is in fair agreement with Sjögren's calculations and which certainly fails to support the above-quoted statement by Dahlberg.

3. **Ichthyosis congenita.** There are usually recognized two forms of congenital ichthyosis, namely, ichthyosis foetalis and ichthyosis congenita larvata, while a third form, ichthyosis congenita tardiva, manifests itself shortly after birth. It is uncertain as to whether these are valid distinctions from the genetic standpoint or whether, again, this is a matter of a principal determinant influenced in its manifestation by important modifiers. Conversely, there could be several different genetic bases for each of these three categories, although there is no evidence in that direction at the present time. Most cases of ichthyosis of early infancy fall into the ichthyosis congenita larvata group. Cockayne (1933) tabulated the case reports of this latter condition which were available to him from the standpoint of parental consanguinity. Almost all these reports concerned European material. In a total of 92 sibships for which there was complete information concerning the sibship (discarding from his tabulation the two Japanese sibships reported by Matsumoto), there was no statement concerning consanguinity in 44, no known consanguinity in 19, a first cousin relationship in 22, and other consanguineous relationship in 7. The incidence of first cousin marriages thus lies between 0.24 and 0.46. It would seem reasonable to assume that in some cases where there is no statement concerning consanguinity, this matter has been investigated, found negative, and overlooked in the preparation of the manuscript, i. e., although there are undoubtedly cases of first cousin marriage among the group for which there is no statement, the incidence is not so high as where the question has been specifically answered. We shall assume, somewhat arbitrarily, that the value of k is in the neighborhood of 0.35, probably falling between 0.30 and 0.40.

The Japanese data are again quite limited. Of the seven sibships pictured by Komai (1934, 1947), six are the outcome of consanguineous marriage. Yamamoto and Ishikawa (1939), in a discussion of ichthyosis in which the above mentioned classification was followed, report that of 10 sibships for which information was available concerning parental consanguinity, 8 were the outcome of first cousin marriage. As shown in table 6, the corresponding gene frequency is in satisfactory agreement with the European values.

4. **Congenital total color-blindness.** Despite the significant clinical variations in the manifestations of this trait, we shall, for purposes of calculation, regard the group as genetically homogeneous, although it is possible that total color-blindness without associated ocular symptomatology falls into a separate category. The data concerning consanguinity in the parentage of European cases of total color-blindness are poor. Peter (1926) in a survey of the literature to date states that there was parental consanguinity for 14 of 60 segregating sibships, but emphasizes that because of poor reporting this represents a very minimal figure. Three of the 14 consanguineous unions were marriages between first cousins; four of the 14 involved consanguinity of a degree not stated. Peter does not list the papers on which this statement is based. The lower limit of first cousin marriages in this data is thus 0.05 to 0.12. Of the 39 segregating sibships figured by Bell (1933), four are the result of a first cousin union, three of consanguineous unions stated to be other than first cousin, six of consanguineous unions the degree of which is not stated (one definitely second cousin or more remote), 12 of non-consanguineous matings, and 14 of matings for which there is no clear statement regarding consanguinity. The lowest incidence of first cousin marriage is thus 0.11 while the highest is 0.36. Göthlin (1941) states that parental consanguinity was present in 13 of 40 well studied sibships reported in recent years by himself and other authors

—assuming that half of these consanguineous unions involved first cousins, this is an incidence of 0.16. Despite these discrepancies, it appears that the incidence of first cousin marriages in this material is somewhat less than in the parentage of several of the other diseases which we have discussed—for purposes of calculation we will adopt a value of 0.16, with the true value probably lying between 0.11 and 0.21.

Three Japanese summaries are worthy of mention. Hohki (1941, quoted from Göthlin) was able to locate reports of 89 cases in 44 sibships, 0.47 the offspring of first cousin unions. Hitomi (1943) in his summary listed 67 segregating sibships, with the parents definitely first cousins in 23 instances, and quite probably so in even more, since the degree of consanguinity was not always clearly stated. This is a minimum incidence of 0.34. Komai (1934, 1947) records 69.2% consanguinity in the parentage of 26 segregating sibships. A figure of 0.45 seems a not unreasonable estimate of the frequency of first cousin marriages in the parentage of these individuals, with the true values possibly between 0.39 and 0.51. There is satisfactory agreement between the corresponding estimates of gene frequency in the two populations. There are no satisfactory estimates of the frequency of this disease in the general population. Göthlin (1924) has very tentatively suggested an incidence of 1:300,000 in Sweden. The gene frequency figures, on the other hand, would suggest that the condition is somewhat more common.

5. **Xeroderma pigmentosum.** This rare disease is so striking that in the past a relatively high proportion of the cases seen in European medical centers have probably found their way into the literature. The condition appears to depend on a very specific alteration in metabolism which might have several different genetic bases but most probably has only one. The authoritative summary of Siemens and Kohn (1925) has been added to by Cockayne (1933) and by Macklin (1936). A total of 417 cases in 265 families had been reported up to 1933. Siemens and Kohn (1925) have pointed out that if all the reported cases are divided into those reported prior to 1906, and those recorded later, consanguinity is more common in the latter; this is probably a consequence of more thorough investigations in recent years. There is some evidence that the condition occurs more commonly in the offspring of marriages between Jews, and the consanguinity figures for this group may be different. Siemens and Kohn (1925) concluded that the true incidence of first cousin marriages in the parentage of the cases reported up to 1925 lay between 0.11 and 0.47. The first figure corresponds to the percentage of first cousin marriages in all the material, while the second corresponds to the incidence of first cousin marriages in the cases reported since 1906 for which there is a definite statement as to presence or absence of consanguinity. When allowance is made for the inclusion of Jewish cases, the true figure for the Gentiles in this material may not lie far from 0.25. Of the 43 cases summarized by Cockayne which have appeared since the paper by Siemens and Kohn, 10 may be discarded as occurring in Arabs, Jews, or Japanese. In the remaining 33, four were the offspring of first cousins, five of other consanguineous mating, for six there was no relationship, and for 18 there was no statement. The incidence of first cousin marriage in this group thus lies someplace between 0.12 and 0.27, with 0.20 being a not unreasonable figure. For purposes of calculation, then, we may assume that about 0.23 of the parents of individuals with xeroderma pigmentosum are first cousins.

The Japanese data are fairly extensive, and present the same problems as do the European. Komai (1947) presents only 13 sibships, five the outcome of consanguinity. However, Kawakami (unpublished) in a careful survey of the Japanese literature has found since 1894 reports of 382 cases in 252 sibships. Of these 252 sibships, 46 were the outcome of first cousin marriage, 10 were the outcome of consanguineous marriages of a degree stated to be other than first cousin, 25 were the result of consanguineous marriage the degree of which was

not stated, in 36 instances the parents were not consanguineous, and for 135 there was no statement. The true incidence of first cousin marriage in the parentage of this material thus lies between 0.18 and 0.61 (assuming in the latter figure that the 25 consanguineous marriages where the degree was not stated were all first cousins). An estimate of 0.40 for purposes of calculation would not seem to be unreasonable.

Table 6 shows that for the gene responsible for xeroderma pigmentosum, alone of the five studied, there appears to be a discrepancy between European and Japanese figures, with the gene more common in Japanese. This finding receives some support from the relative volume of Japanese publications on the subject, as well as the impressions of Japanese clinicians.

The Rate of Appearance of Induced Recessive Mutations in European and Japanese Populations

Haldane (1947) has touched upon the problem of the temporal distribution of recessive phenotypes due to mutations induced in a brief period during the life span of a single generation, as by an atomic bombing, in a population in which a certain degree of heterozygosity already exists. In his calculations he assumed an α value of 0.001, i.e., the value found by Orel (1932) plus "allowance" for consanguinity present but undetected. It is of interest to consider briefly the effect of a higher α value on this temporal distribution. If we deal with only a single genetic locus, represented in the population by two alleles, A, the (dominant) normal, and a, a (recessive) derivative, then in a panmictic population in genetic equilibrium, the following approximate relationship obtains:

$$m = (1 - f)[\alpha q + (1 - \alpha)q^2]$$

or, restated in terms of q,

$$q = \frac{-\alpha(1 - f) + \sqrt{(1 - f)^2\alpha^2 + 4m(1 - \alpha)(1 - f)}}{2(1 - f)(1 - \alpha)}$$

where α = the mean coefficient of inbreeding,

q = the frequency of the recessive allele under consideration,

m = the natural mutation rate from A to a per gene per generation, assumed at 1×10^{-5}, and

f = the relative fertility of individuals homozygous for the recessive allele under consideration ($f = 1$ in absence of selection), here assumed at 0.5.

This is undoubtedly an oversimplification of any situation which might be encountered in nature, since, to mention only two of the known complications, on the average each genetic locus is represented by more than two alleles, and reverse mutation from $a \rightarrow A$ is not incorporated into the equation. The latter will usually be a negligible factor and can safely be neglected.

With these assumptions, equilibrium in a population where $\alpha = 0.00060$ (the observed value for a European population) will be reached at $q = 0.00418$.

When $\alpha = 0.00372$ (as in the Japanese population investigated) equilibrium will be reached at the lower q value of 0.00299. The frequency of the recessive phenotype will of course be the same in the two populations, namely, 0.00001. The tentative calculations of gene frequency in the preceding section have, however, failed to suggest the gene frequency differences demanded by the equilibrium formula. The explanation of this is in all probability to be sought in the fact that the relaxation of inbreeding characteristic of present day European populations is of so recent origin in terms of generations that it has not yet been reflected to an appreciable extent in gene frequencies (cf. Haldane, 1939). Therefore, in a consideration of the comparative genetic effects of an atomic bombing we may start with the fact that, so far as can be determined at present, the frequency of highly undesirable recessive genes is approximately the same in Japanese and European populations, being in both populations at a level fixed by a much higher incidence of consanguinity than obtains in present-day European populations, with the corollary that because of a higher incidence of inbreeding the traits themselves are actually more common in the Japanese. This is not to infer, however, that the present Japanese population is in genetic equilibrium. It is probably more nearly so than European and American populations, but there are still many factors to disturb the genetic balance. Yet for the grossly unfavorable recessive genes, there has probably been a sufficient approach to equilibrium in the past to render permissible in a first approximation the use of the equilibrium formula to calculate the approximate frequency of recessive genes meeting certain requirements.

The effectiveness of irradiation in producing mutation in human genes is unknown From analogy with the results in non-human material, we may assume, following the treatments of Haldane (1947) and Evans (1949), that the chance of mutation per gene per r in mature gametes is of the order of 2×10^{-8}. Then in a population of 100,000 survivors of an atomic bombing, each survivor having received on the average a dose of 100 r, the probability of an induced recessive mutation at the locus under question in any gamete is $100 \times 2 \times 10^{-8}$, or 2×10^{-6}. This calculation involves the assumption that gonial cells, the source of gametes in the reproductive years following an atomic bombing, have the same sensitivity to irradiation as mature gametes, a point concerning which there are no exact data for mammals at the present time. Thus, in a population where q may be assumed originally to equal 0.003, the result of an atomic bombing as described above will be to increase q to 0.003002, i.e., the chance is 1 in 5 that in a population of 100,000 some one individual will have an induced recessive mutation at the particular locus under discussion. The assumed contribution of $100r$ to the total heterozygosity of the population is relatively small, and is only one-fifth that deriving each generation from the assumed spontaneous mutation rate for this locus. In connection with this statement, however, attention should be called to the unsatisfactory state of our knowledge

concerning human spontaneous mutation rates; the figure of 10^{-5} per gene per generation used in this paper is the best approximation from a scanty data.

Haldane (1947) has pointed out that once the natural equilibrium which regulates gene frequencies has been disturbed by such an event as an atomic bombing, the return to equilibrium values will in a population where $\alpha = 0.0010$ require thousands of generations, with the rate at which recessive zygotes are to be expected rising in 200 years or less to a level somewhat in excess of $\frac{1}{2}\alpha$ if there is already considerable heterozygosity at the locus in question—which will usually be the case. Where the coefficient of inbreeding is six times higher, as in the present Japanese population, we may expect that the return to equilibrium will be accelerated, but the genetic effects of the bombing, being distributed over fewer generations, will be correspondingly more obvious. Thus, following Haldane (1947), we may, disregarding selection and making assumptions as shown, calculate the "peak" genetic effect for an assumed particular locus in the two populations as follows:

MEAN COEFFICIENT OF INBREEDING α	INITIAL GENE FREQUENCY q	INCREASED GENE FREQUENCY $q + \Delta q$	INITIAL FREQUENCY OF RECESSIVES $\alpha q + (1 - \alpha)q^2$	INCREMENT RECESSIVES $\Delta q(\alpha + 2q)$	"EQUILIBRIUM" FREQ. OF RECESSIVES BEFORE SELECTION
.001	.003	.003 002	.000 011 991	.000 000 014	.000 012 005
.006	.003	.003 002	.000 026 946	.000 000 024	.000 026 970

As a result of this greater degree of inbreeding there will therefore be at the peak of the curve approximately twice as great an absolute effect when $\alpha = 0.006$, although the proportionate effect will actually be smaller. But in either case, the obvious impact on the population of induced mutation at this particular locus will be small indeed, amounting at the peak to about 1.4–2.4 individuals showing the trait per 100,000,000 persons. The total impact of the recessive mutations produced by an atomic bomb on two such populations will be the summation of the genetic effects on thousands of loci, differing among themselves as to initial frequency of recessives, sensibility to irradiation, selective disadvantage of the homozygote, etc. If there were 30,000 loci each behaving as in the illustration above—a situation contrary to fact but useful for purposes of illustration—at the peak effect there would be 30,000 × 1.4–2.4 per 100,000,000, or on an average 4.2–7.2 per 10,000 persons showing the effects of an induced recessive mutation.

DISCUSSION

The observation that the average coefficient of inbreeding is some six times as high in present day Japan as in comparable European populations immediately suggests the possibility of certain genetical consequences of this fact. However, attempts to utilize these data in various types of calculations rapidly

leads to issues of some complexity. We realize fully the errors inherent in the relatively crude methods utilized here, and the sources of criticism. However, even if refined mathematical methods did exist, it is doubtful whether the data available for European and Japanese populations would justify their application. It is hoped that this communication has further emphasized a fact already recognized by many students of human genetics, namely, that the weaknesses which exist in the present day data concerning the genetics of human populations are no less extensive than the weaknesses in our mathematical tools for dealing with better data if they did exist. Valid studies of gene frequencies by indirect methods are as dependent upon an improvement in the quality of case reports and our knowledge of the breeding structure of human populations as on developments in mathematical theory. But when all due apologies have been made, the interesting fact remains that this first crude approach reveals in four out of five recessive abnormalities considered no apparent differences in gene frequencies between the European and Japanese populations. Despite the large errors of estimation, it appears that the four genes whose frequencies have been found to agree in the two populations differ significantly among themselves as to incidence, i.e., in both populations the genes responsible for achromatopsia and albinism are almost certainly more common than those which produce ichthyosis congenita and infantile amaurotic idiocy. The frequency seriation thus established corresponds with what is known or may be surmised regarding the selective disadvantage which these four genes confer upon homozygotes. Thus, for infantile amaurotic idiocy and ichthyosis congenita larvata f is and almost certainly has for centuries been zero. For congenital total color-blindness and albinism f is probably at the present time in the neighborhood of 0.7–0.8, but it seems probable that in past centuries the value has been more like 0.4–0.5, and this latter value is the one which has determined the present-day gene frequency. It is possible that the greater apparent frequency in Japanese of the fifth gene, xeroderma pigmentosum, is due to a higher f value in consequence of the skin pigmentation difference, although a different mutation pressure of course cannot be ruled out.

The estimation of the rate of mutation of recessive or incompletely recessive genes is fraught with many pitfalls. Not the least of these is the necessary assumption that the species is in approximate equilibrium with respect to the genes in question. Because of the relatively recent decrease in the intensity of inbreeding in most countries of the world, this assumption will be incorrect for most bodies of data. The error introduced by the assumption should be small in the case of such relatively common genes as those responsible for thalassemia in Mediterranean peoples or sickle cell anemia in Negroes, and increase in inverse proportion to the frequency of the gene. In the case of the first four genes under consideration in this paper, the estimates of mutation rate vary widely depending on whether one uses an α value of 0.001 or 0.006. Thus if for albinism

and congenital total color blindness we assume an f value of 0.5 and a q value of 0.005, at the assumed European α value of 0.001, m is 1.5×10^{-5}, while at the Japanese value of 0.006, m is 2.8×10^{-5}. Similarly for infantile amaurotic idiocy and ichthyosis congenita, with f values of zero and q values of 0.0015, m is 4×10^{-6} at an α value of .001 and 11×10^{-6} at an α value of .006. Although racial differences in mutation rate are certainly a possibility, it seems more likely that the apparently lower mutation rates in Caucasians reflect the relaxation of inbreeding, so that the Japanese values are very significantly more accurate than the Caucasian. These Japanese values of 2.8×10^{-5} and 1.1×10^{-5}, fall well within the range of estimates of human mutation rates.

It is a pleasure to acknowledge the aid we have received from Dr. C. W. Cotterman in the treatment of some of the statistical problems discussed herein.

CONCLUSIONS

1. The incidence of consanguineous marriage in Japan has been investigated in three cities, Hiroshima, Nagasaki, and Kure, and in two special areas, an Eta village (Midori Machi) and a fishing settlement (Dainu). Among women currently registering their pregnancies for ration purposes, the percentage married to first cousins was 3.71 in Hiroshima (10,547 marriages), 4.10 in Kure (5,510 marriages), and 5.24 in Nagasaki (7,747 marriages). A survey of all marriages in selected sectors of two of the cities revealed first cousin marriages in 3.93% of 3,283 Hiroshima unions, and 4.64% of 1,642 Kure unions. In the two special areas, first cousin marriages occurred in 5.44% of 147 Midori Machi unions and 7.12% of 323 Dainu unions. The mean coefficient of inbreeding in Hiroshima and Kure is 0.00372, some six times that of the only urban European population studied in this respect.

2. Utilizing the theoretical relationship which exists under conditions of panmixia between gene frequency, consanguinity in the general population, and consanguinity in the parentage of individuals with recessively inherited diseases, very tentative calculations are made of the frequencies in European and Japanese populations of the recessive genes responsible for five diseases, namely, albinism, infantile amaurotic idiocy, achromatopsia, ichthyosis congenita, and xeroderma pigmentosum, assuming in each case a monogenic determination of the trait in question. It is emphasized that deviations from panmixia as well as deficiencies in the data very seriously limit the confidence which may be placed in the results of these calculations, so that the results may be regarded only as a first approximation. It is found that the frequencies of four genes show a tolerable correspondence in the two groups, while one gene, xeroderma pigmentosum, may be more frequent in the Japanese.

3. Induced recessive mutations may be expected to manifest themselves significantly more rapidly in Japanese than in European populations if this difference in the coefficient of inbreeding persists.

REFERENCES

BARTELS, E. D. 1941. Heredity in Graves' disease. *Opera ex Domo Biol. Hered. Human. Univ. Hafn.* vol. 2. Copenhagen: E. Munksgaard. pp. 384.

BELL, J. 1926. Colour-blindness. *Treasury of Human Inheritance*, vol. 2, part 2. Cambridge: University Press. pp. 125–267.

BELL, J. 1940. A determination of the consanguinity rate in the general hospital population of England and Wales. *Ann. Eugen.*, Cambr. 10: 370–391.

BÖÖK, J. A. 1948. The frequency of cousin marriages in three North Swedish parishes. *Hereditas*, 34: 252–255.

BRENK, H. 1931. Über den Grad der Inzucht in einem innerschweizerischen Gebirgsdorf. *Arch. Julius Klaus. Stift.* 6: 1–39.

COCKAYNE, E. A. 1933. *Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press. pp. x, 394.

DAHLBERG, G. 1938. On rare defects in human populations with particular regard to inbreeding and isolate effects. *Proc. R. Soc. Edinburgh*, 58: 213–232.

DAHLBERG, G. 1948. *Mathematical Methods for Population Genetics*. London, New York: Interscience Publishers. pp. viii, 175.

DUNN, L. C. 1947. The effects of isolates on the frequency of a rare human gene. *Proc. Nat. Acad. Sc., U. S.* 33: 359–363.

EGENTER, A. 1934. Über den Grad der Inzucht in einer Schwyzer Berggemeinde und die damit zusammenhängende Häufung rezessiver Erbschäden. *Arch. Julius Klaus. Stift.* 9: 365–406.

EVANS, R. D. 1949. Quantitative inferences concerning the genetic effects of irradiation on human beings. *Science*, 109: 299–304.

GATES, R. R. 1946. *Human Genetics*. New York: Macmillan Co. 2 vols. pp. xvi, 1518.

GÖTHLIN, G. F. 1924. Congenital red-green abnormality in colour-vision, and congenital total colour-blindness, from the point of view of heredity. *Acta ophth.*, Kbh. 2: 15–34.

GÖTHLIN, G. F. 1941. Die Erblichkeit angeborener totaler Farbenblindheit mit Lichtscheu. *Acta ophth.*, Kbh. 19: 202–218.

GROB, W. 1934. Aszendenzforschungen und Mortalitätsstatistik aus einer st. gallischen Berggemeinde. *Arch. Julius Klaus. Stift.* 9: 237–264.

HALDANE, J. B. S. 1939. The spread of harmful autosomal recessive genes in human populations. *Ann. Eugen.*, Cambr. 9: 232–237.

HALDANE, J. B. S. 1947. The dysgenic effect of induced recessive mutations. *Ann. Eugen.*, Cambr. 14: 35–43.

HALDANE, J. B. S., & MOSHINSKY, P. 1939. Inbreeding in Mendelian populations with special reference to human cousin marriage. *Ann. Eugen.*, Cambr. 9: 321–340.

HITOMI, K. 1943. On the heredity of total color-blindness. *Minzoku Eisei* (*Japanese Journal of Racial Hygiene*), 11: 427–441.

HOGBEN, L. 1946. *An Introduction to Mathematical Genetics*. New York: W. W. Norton. pp. xii, 260.

KATSUNUMA, MURAKAMI, & TAKESITA. Unpublished manuscript.

KIDA, F., KANOKOGI, K., & KOJIMA, T. 1949. A study on consanguinity and affinity. *Iden* (*Heredity*) 3: 135–139.

KOMAI, T. 1934. *Pedigrees of Hereditary Diseases and Abnormalities Found in the Japanese Race*. Tokyo: Maruzen Co., pp. iv, 51.

KOMAI, T. 1947. *Pedigrees of Hereditary Diseases and Abnormalities Found in the Japanese Race (1934–1943)*. Tokyo: Hokuryukan. pp. 225.

KURASIMA, M. 1937. Albinism in Gifu-Prefecture. *Nagoya J. M. Soc.* 46: 33–53.

LENZ, F. 1919. Die Bedeutung der statistisch ermittelten Belastung mit Blutverwandtschaft der Eltern. *Münch. med. Wschr.* 66: 1340–1342.

MACKLIN, M. T. 1936. Xeroderma pigmentosum, an inherited disease due to recessive determiners. *Arch. Derm. Syph.*, Chic. 34: 656–675.

AUF DER NÖLLENBURG, W. 1932. Statistische Untersuchungen über die Erblichkeit der Lebenslänge. *Zschr. menschl. Vererb.* 16: 707–755.

OREL, H. 1932. Die Verwandtenehen in der Erzdiözese Wien. *Arch. Rassenb.* 26: 249–278.

PEARSON, K., NETTLESHIP, E., & USHER, C. H. 1911–1913. A monograph on albinism. Draper Company Research Memoirs, Biometric Series VI and IX. London: Dolan & Co., Ltd.

PETER, L. 1926. Zur Kenntnis der Vererbung der totalen Farbenblindheit mit besonderer Berücksichtigung der in der Schweiz bis jetzt nachgewiesenen Fälle. *Arch. Julius Klaus. Stift.* 2: 143–189.

REUTLINGER, W. 1922. Über die Häufigkeit der Verwandtenehen bei den Juden in Hohenzollern, und über Untersuchungen bei Deszendenten aus jüdeschen Verwandtenehen. *Arch. Rassenb.* 14: 301–305.

ROBERTS, J. A. F. 1932. Human pathological conditions determined by any one of several genes. *Nature*, Lond. 130: 542–543.

RUEPP, G. 1935. Erbbiologische Bestandesaufnahme in einem Walserdorf der Voralpen. *Arch. Julius Klaus. Stift.* 10: 193–218.

SIEMENS, H. W. & KOHN, E. 1925. Studien über Vererbung von Hautkrankheiten. IX. Xeroderma pigmentosum. *Zschr. indukt. Abstamm.* 38: 1–61.

SJÖGREN, T. 1931. Die juvenile amaurotische Idiotie. *Hereditas*, 14: 197–418.

SJÖGREN, T. 1948. Genetic-statistical and psychiatric investigations of a West Swedish population. *Acta psychiat. neur.*, Kbh. 52 (Suppl.): 1–102.

SLOME, D. 1933. The genetic basis of amaurotic family idiocy. *J. Genet.* 27: 363–376.

SNYDER, L. H. 1947. The principles of gene distribution in human populations. *Yale J. Biol.* 19: 817–833.

SPINDLER, A. 1922. Über die Häufigkeit der Verwandtenehen in drei württembergischen Dörfern. *Arch. Rassenb.* 14: 9–12.

WEINBERG, W. 1920. Methodologische Gesichtspunkte für die statistische Untersuchungen der Vererbung bei Dementia praecox. *Zschr. ges. Neur. Psychiat.* 59: 39–50.

WULZ, G. 1925. Ein Beitrag zur Statistik der Verwandtenehen. *Arch. Rassenb.* 17: 82–95.

YAMAMOTO, H. & ISHIKAWA, M. 1939. On the hereditary relation in congenital ichthyosis. *Oosaka Iji Shinshi* (*Oosaka Medical Journal*) 12: 1–10.

Turner's Syndrome and Status Bonnevie-Ullrich

A Synthesis of Animal Phenogenetics and Clinical Observations on a Typical Complex of Developmental Anomalies

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BREEDING experiments and systematic embryological studies of developmental processes are not feasible in human genetics. Hence, human physiological genetics must be based in large part upon principles which can be learned from experimental genetics. On the general applicability of basic genetic laws there is no longer a question. But, just as the mechanism of simple and complex Mendelian transmission can be verified in man in full detail, it is also becoming increasingly evident that there is a parallelism in the *modus operandi* of certain genes in both man and animal. Since certain key genes undoubtedly play identical, or at least very similar, roles in the organizational plans of various higher organisms, it is understandable that the mutations of these genes should likewise have followed similar pathways. Even peristatic (i.e., intrauterine environmental) factors can exert themselves in embryogenesis in a manner simulating the action of mutant genes. Therefore, in developmental pathology, as in developmental physiology, a striking similarity is again apparent between man and higher animals. Our knowledge of homologous hereditary variations showing a similar genetic basis and developmental course in various mammalian species and genera is steadily growing. Thus comparative phenogenetics opens up a broad field of investigation for human biology and genetics.

Especially suited for studies of this kind are the various abnormalities of general body form. To be sure, we need to forewarn ourselves against the dangers of inferring homologous genetic events for single characteristics. For we have learned from general genetics that phenotypically very similar traits can not only be due to different genes, but can also result from entirely different epigenetic events. However, the probability of drawing erroneous analogies is somewhat reduced in the case of complex characteristics. And, if a key to the understanding of apparently disconnected multiple anomalies can be acquired from observations of experimental animals, it is entirely appropriate to transfer knowledge gained in this way to an analysis of the phenogenesis of human anomaly-complexes.

Among the more highly organized species, man is the best studied with respect to teratology. A gigantic store of observation is available on human multiple anomalies or "syndromes", which morphologically can be analyzed in

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minute detail. Their formal development, however, can at best be retraced into fetal life; events falling within the embryonic period can be reconstructed only in very limited measure through systematic investigation. It is here that the teachings of comparative pathological genetics can serve as a stepping stone, since it is precisely in embryonic development that the various mammalian species show the most far-reaching analogies. Whenever it is thus possible to find in the phenogenetic processes of an animal a connection with a human syndrome, it is not essential for its extension to human genetics that there be found an exact morphologic correspondence of the end products. Even in the case of completely homologous developmental processes one may expect differences in the general plan of organization to produce certain deviations in the final mode of expression. Thus the desired synthesis demands to a considerable degree an inquiry into the phenogenetic mechanism starting from both the initial and the final stages of the process.

In the following pages a typical complex of anomalies, *Status Bonnevie-Ullrich* (St.B.U.), will serve to illustrate the various possibilities of interpretation that are afforded by a comparative analysis of developmental mechanics in the animal and clinical observations on man.

THE BAGG-LITTLE MOUSE MUTATION, "MYELENCEPHALIC BLEBS"

In what proved to be a trail-blazing discovery in the field of mammalian phenogenetics, Kristine Bonnevie (1932, 1934) was enabled by a discerning combination of genetic experiments and embryological analysis to reach a flawless clarification of the formative events underlying various multiple anomalies in an abnormal strain of the house mouse. The mutation analyzed by her was one recovered by Bagg and Little (1924) from a race of inbred, x-rayed mice. It proved to be a monogenic recessive abnormality manifesting itself in the form of very diverse *malformations of the head and extremities.* The eye defects consisted principally in a narrowing of the palpebral fissures, sometimes associated with a reduction in the size of the globe (microphthalmia) and a twisting of the snout to the same side (fig. 4). Also the ears were variously deformed;

FIGS. 1–5. Abnormalities in embryos and adults of the "myelencephalic bleb" mutation in the house mouse (Bagg-Little).

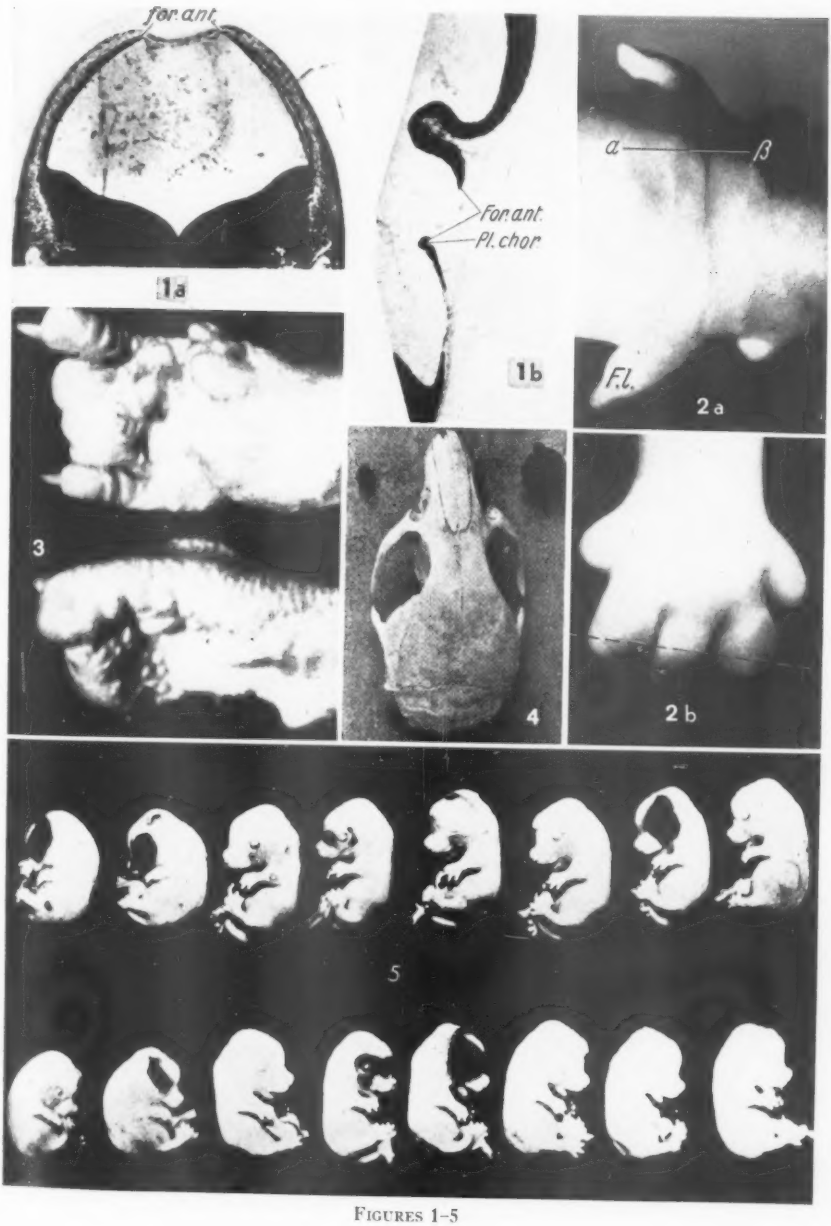
FIG. 1. *a.* Cross-section; *b.* Sagittal section through the myelencephalon in the 7 mm. embryo, showing *foramen anterius* (for. ant.). After Bonnevie, 1934.

FIG. 2. *a.* Primary blebs of the neck and shoulder region in a 10 mm. embryo; *b.* Blebs of the hind foot. After Bonnevie, 1934.

FIG. 3. Severe foot deformities in Bagg-Little mice. After Bonnevie, 1934. (Compare with figs. 6, 8 and 9.)

FIG. 4. Atrophic left eye and asymmetry of skull due to bleb of the left side of head. After Bagg and Little, 1924.

FIG. 5. A litter of 8 young resulting from a mating of two *my/my* mice, showing localization of blood-filled blebs of the head region. Left and right sides of each embryo are shown. After Bagg and Little, 1924, in the *American Journal of Anatomy.*



FIGURES 1–5

FIGURES 6–9

unilateral or bilateral microtia were not uncommon. The anomalies of the limbs were very diversely comprised of syndactyly, polydactyly, hypodactyly, and severe clubbing defects, such defects being *usually unilateral*, more common on the left side than on the right, and much more frequent and *more severe in the forefeet than in the hindfeet.*

By means of extensive studies on hundreds of embryos of all stages, Bonnevie was able to trace the origin of these multiple defects to an exudation of cerebrospinal fluid beneath the skin of the neck. In normal mouse embryos of 7–8 mm. this fluid, already being formed in the myelencephalon, escapes through a transitory opening in the roof of the primitive fourth ventricle, the *foramen anterius* (fig. 1), and collects beneath the epidermis, where it is absorbed. In the abnormal Bagg-Little embryo, however, an excess quantity of cerebrospinal fluid collects in the neck region in the form of a large bleb or blister (fig. 2*a*). These primary neck blebs (*Nackenblasen*) then migrate beneath the epidermis—guided by the surface relief and conditions of tension in the embryonic skin—over the lateral portions of the head into the face (fig. 5), and over the trunk into the extremities (fig. 2*b*). Through stagnation in the concave areas, such as the orbital pits, or after arrestment at the ends of the limb buds, the increased pressure resulting from subsequent transudation of blood and lymph leads to the disruption of formative processes in their sensitive phases and hence to persisting anomalies. Wandering blebs leave scarcely any trace of their paths, these being detectable at most by a somewhat sparse growth of the hairy coat. Also, in places where gross deformities are produced through the pressure of arrested blebs, the fluid is usually wholly resorbed during the fetal period.

On the basis of Bonnevie's studies, this syndrome in the mouse was later termed "myelencephalic blebs" by Little and McPheters (1932), the recessive gene being labelled *my*. For further details and references to the extensive literature the reader is referred to summaries by Grüneberg (1943, 1947).

THE ASYMMETRIC FORM OF STATUS BONNEVIE-ULLRICH

This astonishing revelation of the formative processes responsible for multiple anomalies in Bagg-Little (*my*) mice was utilized by me in 1936 for the elucidation of very similar complexes of deformities in man. Entirely new reference points were thus established for the interpretation of a seemingly inex-

FIG. 6. Severe malformation of hand in form of symbrachydactyly, combined with unilateral Pectoralis defect. After Steche, 1905.

FIG. 7. Congenital ophthalmoplegia (combined bilateral facialis-abducens paralysis), associated with ptosis, narrowing of the palpebral fissures, and unilateral defect of the Pectoralis. After Peritz, 1912.

FIG. 8. Asymmetric form of St. B. U. in an 18 month-old boy: right-sided Facialis paresis, asymmetry of thorax, with Pectoralis defect and hypoplasia of the nipple, unilateral shortening of the arm, with brachydactyly and syndactyly of the hand, and ogive palate. After Petersen, 1939.

FIG. 9. Congenital right-sided facialis paralysis, with deformed right ear and right upper extremity. After Essen-Möller, 1928.

plicable maze of facts found in the case-history literature on congenital absence of muscles and congenital motor disturbances of the cranial nerve domain. As in all other developmental anomalies, no unitary concept of pathogenesis dared be postulated for these two groups of defects, as was evident from a purely morphological classification. However, a close relationship between certain forms of muscle defects of the trunk and congenital disturbances in the cranial nerve region could be deduced from the fact that they were not infrequently observed in combination. Furthermore, they are often accompanied by still other anomalies of a sort suggesting a common teratologic origin of the two groups of defects.

The typical *unilateral Pectoralis defects* are regularly associated with *hypoplasia or aplasia of the nipple* and a generalized atrophy of the overlying skin and its appendages (sweat glands, hair follicles). Rather frequently they are combined with more or less profound *deformities of the hand* on the same side. *Motor defects in the cranial nerve region* are likewise encountered in association with atrophy of the skin, *anomalies of the hair and sweat glands*, *ear deformities*, including microtia, and *defects of the ocular adnexa* (absence of the caruncula lacrimalis, hypoplasia of the tear glands, narrowing of the eye-slits, etc.). There are in the literature not a few cases (e.g. Gütermann, 1902; Schmidt, 1897; Spatz & Ullrich, 1931) in which the multiple defects of the head and trunk regions bear an exceptionally strong resemblance to the anomaly complexes of the *my* mouse. Especially the severe unilateral deformities of the hand (symbrachydactyly) which accompany Pectoralis defects, and the above-mentioned dysplasias of the orbital structures show an almost complete identity with the animal abnormalities clarified by Bonnevie's work (figs. 3 and 6).

With the aid of the bleb mechanism, moreover, all of the other peculiarities of the syndrome under discussion are made intelligible in a striking way. All of the developmental anomalies of the hand in their varying forms—from the "club-hand", corresponding to the embryonic hand-paddle, to the simple cutaneous forms of syndactyly—are also exhibited by *my* mice. And again, just as the *my* anomalies are more frequent and more severe in the fore-limbs, the defects of the feet in man are quite secondary to those of the hands. Nothing is known concerning unilateral Pectoralis defects in *my* mice. Since such defects in man (in contrast to the symmetric muscle aplasias) are never strictly confined to the musculature, but are usually accompanied by defects of the adjacent skin structures and sometimes even by a cleft of the underlying ribs, it has been customary to assume some arresting agent working from the outside; for example, a hammer-like pressure action of the anterior limb bud or the chin might be considered. But it seems much more reasonable to account for these developmental arrests of the Pectoralis in their many variations by the action of a cerebrospinal fluid bleb, which, in the course of its migration from the neck region into the limb bud, may come to rest in the shoulder region.

The bleb theory proves to be particularly illuminating with respect to the polymorphic nature of the anomalies found in conjunction with congenital locomotor disturbances in the cranial nerve region. Functional deficiencies in this area might be equally due to "muscle defects" or to lesions of the nerves or their motor centers (nuclear defects). The Bonnevie theory offers an explanation *par excellence* for all such possibilities of damage, inasmuch as the primary neck bleb develops over the nuclear region of the medulla oblongata and then wanders over the lateral aspects of the head into the face. Thus, there is a good explanation for unilateral facial paralysis combined with a malformed ear (fig. 9). Of great significance is the fact that in cases of "congenital nuclear damage" (Heubner, 1900) there is no primary agenesis in the strict sense. Just as in Heubner's classical demonstration, it was again apparent in a study by Spatz and Ullrich (1931) that the nuclear anlage must have been present but was destroyed at an early embryonic stage. These two important demonstrations were concerned with cases of *bilateral ophthalmoplegia* and combined *abducens-facialis paresis*. The nuclei of these two cranial nerves lie at the base of the rhomboidal sinus, at precisely the place where the primary neck blister forms, so that a pressure effect of the latter would be expected to be most strongly expressed upon these nerves.

Also explained in the finding of Schüssler and Leischner (1944) that combined VI + VII paralysis always involves a complete deficiency of the upper facial region. From the topological relations of the facialis nerve, it is apparent that mechanical pressure damage to the narrowly circumscribed region of the abducens nucleus is scarcely possible without simultaneous injury of the overlying root of the facialis. The further, infranuclear, tracts of the VI*th* and VII*th* nerves offer considerable variety in the possibilities for damage, so that isolated facialis or abducens pareses are also frequently encountered in varying forms (fig. 8).

One further important fact can be deduced independently from a survey of the published case-reports on cranial nerve defects: it is precisely the combined forms of abducens paralysis that are most commonly observed in company with the above-mentioned dysplasias of the orbital structures and also with the "typical" defects of the Pectoralis and the galaxy of associated anomalies (fig. 7). For such associations of "nuclear lesions" and peripheral developmental disturbances a most cogent explanation is provided for the first time in the theory of wandering cerebrospinal fluid blebs.

PTERYGIUM COLLI AND CONGENITAL LYMPHANGIECTATIC EDEMA

In addition to the concordance shown by the human and *my* anomalies in their final phenotypic form and in their aggregations, one can also infer from the available clinical observations a parallelism in their development extending back into fetal life. The transfer of the cerebrospinal bleb mechanism to human

beings was made particularly obvious to me in view of the fact that prior to the publication of Bonnevie's work I had called attention to the curious edematous conditions of the skin which occur as a part of the syndrome involving muscle aplasias and nuclear deficiencies. Starting from the observation of *pterygium colli* in a 6 year-old girl, I discovered from a review of the literature that the formation of such skin folds on both sides of the neck had a connection with so-called *congenital lymphangiectatic edema*, the latter being evidently a forerunner of pterygium colli. The association was described as a "typisches Kombinationsbild multipler Abartungen" (Ullrich, 1930). It included, in addition: deformities of the ears, hypoplasia of the nipples, syndactyly, and dystrophies of the nails, as well as muscle defects and motor disturbances in the cranial nerve area. Later, on extending the bleb theory to human malformations in 1936, I was able to add from the literature (e.g., Wernher, 1843) descriptions of stillborn fetuses showing massive edema of the neck region (fig. 11) of a form like that occurring in *my* mouse embryos—thus extending the similar course of phenogenesis still further backward toward its inception.

It would thus seem that the cerebrospinal bleb mechanism had been established without a gap, commencing with the time of origin of the primary neck blister. Nevertheless, I have pointed out from the beginning that such analogies based upon purely epigenetic events do not prove the presence of an identical starting mechanism. The syndrome in *my* mice has been shown to be recessively inherited; therefore, the excess oozing of cerebrospinal fluid must be conditioned by the action of the abnormal gene in homozygous state (*my/my*). Thus far no definite conclusion has been reached concerning the inheritance of the corresponding syndrome (St.B.U.) in man. Moreover, the transfer of the bleb theory to man does not, of course, demand a genetic determination of the resulting human anomalies. It is at least conceivable that purely peristatic factors might initiate the appearance of excess cerebrospinal fluid.[1]

On purely theoretical grounds, one would expect "wandering cerebrospinal fluid blebs" to produce a kaleidoscopic assortment of defects, in other words, a markedly *polyphenic* syndrome. In assigning the various clinical cases to St. B.U. it is therefore neither essential that inheritance should be demonstrated nor that an exact correspondence should be evident between the human anomalies and those shown by *my* mice. Furthermore, no single characteristic in itself can be regarded as pathognostic. Each individual patient and each anomaly-complex proposed for consideration under St.B.U. must be critically analyzed from both the clinical and phenogenetic points of view. For this purpose I regard the following criteria as significant:

[1] An observation by Liebenam (1938) on twins is of interest in this connection. In a pair of one-egg twin sisters, only one exhibited a complex consisting of unilateral absence of the Pectoralis and severe syndactyly, whereas in respect to a slight scoliosis, a slanting pelvis, and a hypoplastic high swung scapula the twins showed mirrored concordance. From this observation one can infer a strongly modifying action of intrauterine environmental factors.

1. The designation of St.B.U. should be reserved for those multiple deformities or syndromes which, in their form and distribution, are wholly explicable in terms of the bleb mechanism. Since this mechanism permits a certain freedom of expression, isolated anomalies of each type and symmetrical systemic anomalies should not be drawn into consideration here.

2. Within the general group of congenital motor defects in the cranial nerve region and congenital muscle defects it is particularly fitting to consider those involving a combination of nuclear lesions and peripheral muscle aplasias and other typical anomalies. Also, Bonnevie's theory provides the best available explanation for those cases of typical unilateral Pectoralis defects with deformities of the hand, even when unaccompanied by demonstrable anomalies in the head region.

3. A marked involvement of internal structures in any such complex of abnormalities cannot be harmonized with the bleb hypothesis except in special instances, and these must be decided with extreme caution.[2]

4. A most important diagnostic index is furnished by the occurrence of congenital edematous conditions of the neck and extremities, especially when an asymmetric distribution is evident. "Congenital lymphangiectatic edema," however, requires a careful differentiation from other edematous skin conditions of infancy.

Following my detailed formulation of its serviceability for human pathology, it was natural that Bonnevie's remarkable discovery should have been widely employed for the explanation of various syndromes of developmental anomalies. Thus many authors, with or without knowledge of my publications, have extended the circle of abnormalities to be considered under St.B.U. considerably beyond the confines which I originally proposed. Although Bonnevie's theory is especially attractive in relation to the many diverse combinations of deformities of the head and extremities, it cannot be used as a basis for unifying all of these syndromes. The criteria which I have proposed have often been disregarded in assigning individual cases and certain syndromes to St.B.U. In a recent summary paper (Ullrich, 1949) I have undertaken a critical review of this literature. The results can be summarized here only briefly, with the omission of many details.

In no case should the concept of "bleb diseases" be boundlessly extended in the manner attempted by Engel (1940). If one heeds the various criteria set forth above, it is easy to see that the bleb theory is surely misapplied in the case of Pfaundler-Hurler's disease, in Morquio's disease, in Léri's "pleonostéose familiale," in the Moon-Biedl-Bardet syndrome, and in Crouzon's form of craniofacial dysostosis and other types of oxycephaly. Apert's acrocephalosyndactyly is somewhat more pertinent since in this combination of head and limb deformities the latter strongly resemble symbrachydactyly, as observed in cases of Pectoralis defect. The "spoonhand" in Apert's syndrome would seem to be readily attribut-

[2] For example, minor developmental defects of the heart might be explained by the penetration of bleb fluid from the shoulder region into the mediastinum (Glanzmann, 1946).

able to a developmental arrest resulting from a cutaneous cerebrospinal fluid bleb. However, the decided symmetry of this condition and its constant form of expression have led me in agreement with Nachtsheim (1943) and Haase (1942) to expressly dissociate acrocephalosyndactyly from St.B.U. (Ullrich, 1943). Originally I, too, assumed a close relationship between mongoloid idiocy and the syndrome which I defined involving pterygium colli (Ullrich, 1930). Later, however, in transferring Bonnevie's findings to human anomaly-complexes, I found it necessary to revise this view (Ullrich, 1936). Mongolism, because of its generalized symmetrical character, cannot be satisfactorily explained by the bleb hypothesis.

Arthrogryposis multiplex congenita (Stern), which Heijbroek (1941) has attempted to unite with St.B.U., must be excluded as a symmetrical form of mesodermal dysplasia (Niemeyer, 1946). I am also inclined to regard as extraneous 2 cases of "cranio-carpopedal dystrophy" described by Freeman and Sheldon (1938*a*, *b*), despite the associated facial swellings, because of the symmetric nature of the defects of the extremities. Further, it is surely improper to attribute the "hereditary potato-nose" anomaly in Benjamin and Stibbe's family to the Bonnevie mechanism merely because occasional deformities of the hands appear in the family (Nieuwenhuijse, 1942).

Since pterygium colli occupies a central position in this complex of multiple anomalies and together with the antecedent congenital edema of the skin serves as a useful connecting-link between the human and animal anomalies, it is tempting to relate webbed skin formations in other parts of the body to cutaneous cerebrospinal fluid blebs. As in all other developmental defects, however, a winged-skin deformity may result from various phenogenetic causes. In particular, the unilateral or bilateral skin folds of the popliteal spaces (Kopits, 1937; Marquardt, 1938; Aberle-Horstenegg, 1938), in which there are included muscle fibers and nerve trunks, I consider to be unrelated to St.B.U. It is noteworthy that Kieser (1939) was able to demonstrate a relationship with Status dysraphicus (Bremer, 1926, 1929) in a family showing hereditary multiple skin webs, for which he proposed the more specific title, "myelo-osteo-musculo-dysplasia hereditaria." This constitutional disorder also exhibits numerous other phenotypic connections with the complex of St.B.U.: dysplasia of the nipples, funnel chest, contractures of the fingers and toes, extraocular muscle palsy, etc. Clinical differentiation of Status dysraphicus—of which the early manifestations in childhood are as yet little known—and the anomalies due to cutaneous edema can present extraordinary difficulties. However, it is my opinion that the cutaneous bleb theory is not applicable to these multiple deformities of a very different nature.

Among the congenital conditions involving fluid accumulations and stretching of the skin there are two clinical pictures which may be mentioned. They are, however, distinct from St.B.U. by virtue of an extensive involvement of the internal organs. Siegmund (1938) demonstrated in 2 sibs possessing "congenital lymphangiectatic edema" a severe deficiency of the elastic connective tissue generally. This "elastotrypsia" explained not only the looseness of the skin, but also the formation of numerous intestinal diverticula in these individuals. Under the title of "dysencephalia splanchnocystica", Gruber (1934) described a characteristic syndrome of stillborn infants in which there are hernioid changes of the brain and cyst formations of the abdominal organs, combined with anomalies of the extremities. Gruber justifiably considers the bleb hypothesis unsuited for the clarification of these complex anomalies.

THE SYMMETRIC FORM OF STATUS BONNEVIE-ULLRICH

When the developmental mechanism due to Bonnevie is not overextended in theory, but is restricted to those abnormalities which it so plausibly and simply explains, serious objections cannot be raised against its transfer to

human teratology. Nevertheless, in reviewing the pertinent literature I have reached the conclusion that a certain refinement and subdivision is necessary even within the circle of multiple anomalies which I originally regarded as relevant.

As outlined above, I originally considered congenital lymphaniectatic edema (fig. 10) as a part of the typical syndrome described in 1930, and I also regarded the medial hygromas of the neck seen in stillborn fetuses (fig. 11) as a connecting link of great importance for the extrapolation of the wandering

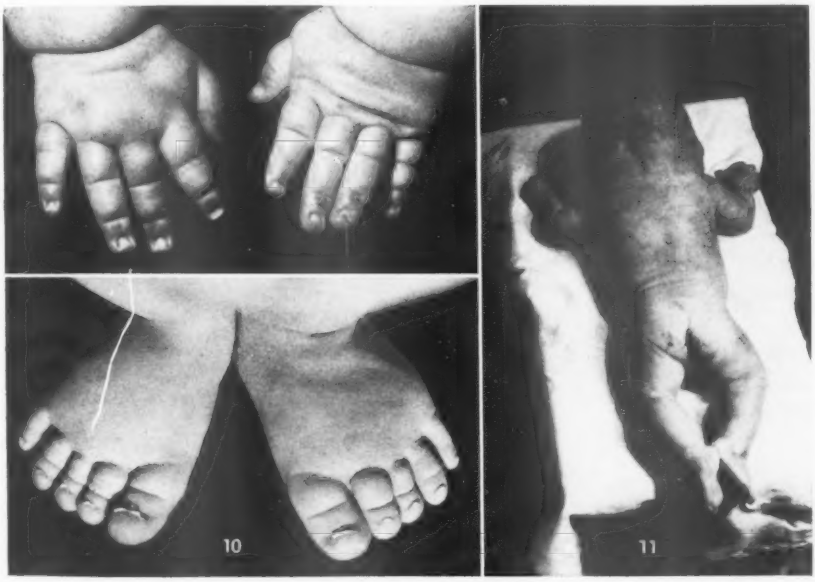


FIG. 10. "Congenital lymphangiectatic edema" of the hands and feet in a female infant, with dystrophy of all nails, especially the toe-nails. After Ullrich, 1938.

FIG. 11. Stillborn fetus with massive edema of the neck and arms. Courtesy of Prof. Rietschel, University of Würzburg Kinderklinik.

bleb mechanism to man. At that time only a few observations were available to serve as examples of the typical syndrome comprising pterygium colli. Meanwhile a large number of cases have since been described (in part as "St.B.U.") which conform without question to the syndrome which I described as a special biotype (fig. 12). The essential features of the complex were independently described above all by Turner (1938) without knowledge of my publications. On the basis of no less than 9 cases, this author characterized as a new syndrome the triad of "infantilism, congenital webbed neck, and cubitus valgus" (fig. 13). On the identity of Turner's

FIG. 12. "Typisches Kombinationsbild multipler Abartungen" [after Ullrich, 1930]. Symmetrical form of Status Bonnevie-Ullrich: pterygium colli, hypoplasia of nipples, deep-set ears, characteristic physiognomy, with ptosis and triangular-shaped mouth.

FIG. 13. Turner's syndrome: Infantilism, webbed neck, and cubitus valgus in 6 female patients. After Turner, 1938, in *Endocrinology*.

FIG. 14. Development of pterygium colli from congenital edema sac of the neck region: *a*. Female newborn with neck edema sac; *b*. Female nursling with broad loose neck folds; *c*. Female, 2 months old, with broad neck skin and diagonal folds in the region of the low-set hair line, combined with lymphangiectatic edema of the extremities and dystrophic nails; *d*. One year-old female, with broad loose neck flaps of the nape congenital lymphangiectatic edema of the hands and feet, and dystrophy of the toe-nails; *e*. (*right*, unlabeled) Eight year-old female with typical pterygium colli (original type case of "Status Bonnevie-Ullrich"). Personal observations.

syndrome and that described by myself prior to the appearance of Bonnevie's reports there can be no doubt. In the description of my original female patient with pterygium colli, mention was made of the small stature and the hypoplasia of the nipples, as well as the cubitus valgus position of the arms (fig. 12). The characteristics emphasized by Turner, on the other hand, recapitulate only some of the more conspicuous features which suffice for the recognition of the complex which I described in greater detail. Since Turner conceived the syndrome as being primarily an endocrine disorder, it is natural that less attention was accorded the less conspicuous anomalies and that the fundamental significance of the congential skin edema was not recognized.

As is so often true of newly described diseases, the further characterization of Turner's syndrome (in the American literature) and Status Bonnevie-Ullrich (in the European literature) followed somewhat different lines. Moreover, due to the limitation of scientific exchange during and since the last war, it was only very recently that the identity of the two described pictures became evident.

On the basis of this literature and further personal observations, the clinical features of this syndrome can now be summarized in the following manner:

By virtue of a relatively constant expression of its component traits, St.B.U. like other "syndromes", is distinctive among the general class of multiple anomalies. The impression created is peculiar to the syndrome alone and permits one at first glance to speak of a special "type". Foremost among the traits responsible for the singular appearance is the *pterygium colli*, the bilateral broad folds of neck skin extending from the shoulders to the mastoid processes, and the resulting illusion of a short neck. The regularly associated moderate dwarfness or *nanism*, the distinct hypoplasia of the nipples and—especially in females—the marked retardation of maturation and the *infantile characteristics* are immediately apparent. Other distinguishing features include: the looseness of the skin (*cutis laxa*), the *low hair-line* at the nape, and the *deep-set ears*; the latter usually show attached lobes and other "degenerative" characteristics, including at times an abnormal channeling of the auditory meatus. Motor defects in the cranial nerve region are hardly mentioned. In particular, there are no reports of asymmetric pareses or combined cranial nerve paralysis, such as the bilateral abducens-facialis type, which might be referred to a lesion in the nuclear area. Nevertheless, the rather languid expression of the entire face, the *sagging eyelids*, which only rarely constitutes an actual ptosis (Ullrich, 1930; With, 1935), the frequent *epicanthus*, and the deep-set corners of the mouth producing a *triangular mouth*, are very prominent. Also characteristic are the dystrophic nails which are usually found on all fingers and toes; these are markedly shortened and perpendicular, and have been described as spoon-nails or *koilonychia* (Glanzmann, 1946; Guinand-Doniol, 1947). With the ex-

ception of the pterygia of the neck, there are as a rule no other web formations, except perhaps between the fingers; numerous, though rather inconspicuous, webs of various interdigital areas have been observed only by Ostertag and Spaich (1936).

Skeletal anomalies are found principally in the head region. In addition to a constantly observed "*ogive palate*", Fanconi and Grob (1934) first drew attention to the marked development of the *impressiones digitatae* of the skull, which Rossi (1945) was able to confirm in almost all of his cases. Another almost invariable symptom in my experience is the *cubitus valgus* deportment of the arms, to which Turner drew attention. Also, a symmetric broadening of the epiphyses of the long bones ("*champignon epiphyses*") seems to be typical (Glanzmann, 1946; Morando, 1946). Unilateral skeletal defects of the lower extremities have been only occasionally encountered: Hoffmann (1937): *luxatio coxae*; Cotterman (1948) *clubfoot*; Guinand-Doniol (1947) luxatio coxae and clubfoot.

Involvement of the internal organs, apart from the gonads (see below), appears to be entirely in the background in the syndrome which constitutes the symmetrical form of St.B.U. Hofmann (1925) assumed the presence of a septal defect in a patient having a systolic murmur; pathologic cardiac findings were also mentioned by Hamne (1948) and Nageotte-Wilbouchewitch (1934). The kidney anomaly in Dreyfus' (1936) case, in which there was assumed to be congenital lues and rachitis (renal form?), need not be related to the syndrome.[3] In contradiction to Rossi and Guinand-Doniol, a review of the entire literature reveals that there is no marked psychic underdevelopment as a rule. The intelligence can indeed be above average in some cases (Turner, personal observations).

At birth, many cases show edematous swellings of the neck and extremities, which gradually subside in the course of the first few months or years. At this early stage, the superfluous skin of the neck region has not yet assumed its final characteristic form. Loose, flabby folds or sacs of skin occur over the nape and throat, and the gradual transformation of these into a typical bilateral pterygium (fig. 14) has been observed in one and the same patient in several instances (Rossi, personal observation). Similarly, there is often a marked edema of the hands and feet or both (fig. 10), which, after its regression, leaves the skin of the fingers and hands (toes and feet) "too loose". Thus, cases described in the literature as "congenital lymphangiectatic edema" can be assigned to the syndrome after careful differential diagnosis with respect to other edematous skin conditions of the newborn.

In a summary paper now in press (Ullrich, 1949), I have assembled from the

[3] It is noteworthy that kidney anomalies occurred in combination with the typical superficial anomalies in several stocks derived from Bagg and Little's mouse strain. Whether these urogenital defects were actually due to the *my* gene was never conclusively determined (Grüneberg, 1947).

German-language literature (including a portion of the observations on "Turner's syndrome") more than 50 cases of St.B.U. This permitted me to strengthen a conclusion already hinted in an earlier paper (Ullrich, 1943), namely, that the syndrome which had at first seemed to me so convincing could no longer be reconciled with an unqualified theory of wandering cerebrospinal fluid blebs. Making use of the criteria listed above, it will be seen that there are unmistakable contradictions from several points of view.

Although the centrally-produced motor defects of the cranial nerve region combined with asymmetric muscle defects and other malformations can be effortlessly aligned with "typical St.B.U.",[4] the constitutional complex corresponding to Turner's syndrome cannot be satisfactorily explained by the wandering bleb mechanism. Thus, the dwarfness, which in older patients is accompanied not only by hypoplasia of the nipples but also by generalized infantilism, cannot be explained without postulating certain ancillary hypotheses which are not at present justified. But above all, the decided symmetrical character of the syndrome comprising pterygium colli stands in clear contradiction to the theory. In fact, it is scarcely conceivable that more or less accidental wandering of cerebrospinal blebs could lead to a symmetrical dystrophy of all fingernails and toenails, as is not uncommonly observed. These facts are not depreciated by the occasional finding of unilateral anomalies, such as foot deformities and dislocation of the hip. Furthermore, the clinical findings in the symmetric form of St.B.U. deviate from the conditions found in *my* mice in that the edema in the former is not dissipated until the first few months or years of life, whereas the cutaneous blebs of *my* mouse embryos are fully resorbed *in utero*. Conversely, in the typical or asymmetric form of St.B.U., there are no cases known to me of edematous skin conditions of the newborn.

These considerations point to certain discrepancies between the asymmetric form of St.B.U. and the symmetric form which is characterized by pterygium colli. Even though such differences might not seem very deep-seated and perhaps even reconcilable, there is one further striking fact which points to a difference in the genetic basis and embryological mechanism: the syndrome including pterygium colli shows a strong predilection for the female, whereas no equally strong bias is evident in the asymmetric syndrome. Among 60 definite cases of pterygium colli and congenital lymphangiectatic edema, I find the sex ratio to be 48 ♀ : 12 ♂. One must consider the possibility that this preponderance of females may result from a preferential recording of female cases due to the more pronounced character of the syndrome in this sex, especially in older patients where there is an evident mammary hypoplasia and sexual underdevelopment. However, this seems to be excluded, since even in

[4] This group has been augmented by important recent observations by Petersen (1939), Schüssler and Leischner (1944), Liebenam (1938), and others.

early childhood females outnumber male cases in the ratio 9:1, and among 13 cases of "congenital lymphangiectatic edema" summarized by Volz (1938), only 3 cases are male, 2 cases being of unspecified sex (table I).

A similar gynectropy, which certainly cannot be ascribed to chance, holds for the cases described under the title of "Turner's syndrome." After writing my more extensive review (Ullrich, 1949), I was enabled through the kind assistance of Dr. C. W. Cotterman to make a survey of the literature from America and other lands:

Martin (1947) gives the sex ratio for Turner's syndrome as 9 ♀ : 1 ♂, and Greenblatt and Nieburgs (1948) report their male patient as being the only exception known to them of the rule that the disease is confined to females, excepting one earlier report by Flavell (1943). However, in the same year Dorff *et al.* (1948) and Foucar (1948) reported two additional male cases, and Foucar cites male patients reported by Sylvest (1940) and Bizzarro (1938). However, the great majority of the described cases are female (Schneider & McCullagh, 6 cases; Turner, 9 cases; Allesandri *et al.;* Greenblatt & Nieburgs' case #1; With; Sharpey-Schafer; Morando; Capurro; Hamne; Shreshevski, 5 cases; Slonimski). It is also noteworthy

TABLE 1. THE SEX DISTRIBUTION IN STATUS BONNEVIE-ULLRICH

REPORTED CASES	FEMALES	MALES
Symmetrical form of Status Bonnevie-Ullrich		
Adults and older children	31	8
Infants and young children	9	1
	40	9
Congenital lymphangiectatic edema (cases of Volz)	8	3
Total	48	12

that the male cases recently added to the literature seem to show a somewhat milder expression of the syndrome (Foucar, Martin, Bizzarro; Martin's own case, however, must be excluded as a case of Klippel-Feil syndrome).

In view of these considerations the question arises as to whether the syndrome comprising pterygium colli, which includes Turner's syndrome, should in any event be classified with St.B.U. In my opinion this may be answered in the affirmative, since the developmental origin of the majority of the anomalies must be referred to fetal edematous conditions of the skin. The question remains, however, whether we are dealing here with "cerebrospinal fluid blebs". To be sure, it is tempting to attribute the massive collection of fluid which gives rise to the pterygium colli to an escape of fluid from the foramen anterius, inasmuch as the latter structure has been demonstrated in the human embryo (Bonnevie, 1934). On the other hand, experimental embryological studies in animals have shown that the formation of unusual skin blisters, which seem to play a role in the etiology of many kinds of anomalies, are not exclusively derived from expressed cerebrospinal fluid.

I shall refer here only to the very careful studies of Sturkie (1941), who was able to trace the origin of naked areas on the head of the domestic fowl to epidermal blisters in the chick embryo, and to the remarkable "blood blisters" of the tips of the tails which Kaven (1943) demonstrated in fetuses of a strain of mice having kinky tails with wedge-shaped vertebrae. Also in Dunn's *st* mutation (1934), a simple recessive form of brachyury combined with locomotor disturbances and deafness, the newborn mice show peculiar blood-filled blisters over the crown of the head and in the neck region. These were subsequently shown by Bonnevie (1940) to arise in a manner entirely different from that of the cerebrospinal blebs of *my* mice.

The developmental physiological theory of Blechschmidt (1947, 1948) also seems worthy of mention in this connection. This anatomist regards conditions of tension in the epidermis, resulting from fluid accumulations within the embryo, to be a fundamental determinant of the general body form. He presumes that the amnionic fluid derives from the embryo by a process of active epithelial transudation, in which the ends of the extremities and the axillae are differentiated as areas of especially active transfer. In personal communication with Prof. Blechschmidt I am told that severe edematous conditions of the neck are "not infrequently" seen in human embryos. The confirmation and further elaboration of Blechschmidt's theory remains for the future.

In any case, it is clear that events other than an oozing of cerebrospinal fluid may lead during embryogenesis to the formation of circumscribed areas of cutaneous edema. In the present stage of the study, I am inclined to regard an autochthonous formation of the skin swellings as a much more probable mechanism for the phenogenesis of pterygium colli than that of wandering "myelencephalic blebs". Since such a mechanism would be not entirely divorced from that of Bonnevie, I do not regard a change in the nomenclature as necessary. Even in the "asymmetric form of St.B.U." it is possible as previously discussed that the phenogenesis is not wholly concordant with that of *my* mice back to the stage of exudation of fluid through the foramen anterius. An autochthonous origin of subcutaneous fluid in symmetrical St.B.U. or Turner's syndrome would imply only that the parallel course of development takes its start at a somewhat later point in prenatal life. Serving to suggest a later teratogenetic determination point, indeed, is the fact that the edematous swellings tend to remain even after birth in the case of the symmetric syndrome, and also the fact that the anomalies produced in the latter tend to be somewhat less severe than those which characterize the asymmetric form of St.B.U.

More important than the problem of nomenclature is the certain conclusion that the establishment of two different phenogenetic mechanisms requires that the two clinical pictures be kept separate for the purpose of further genetic and embryological studies. For such studies a genetically uniform substrate is, of course, an unconditional prerequisite. In contrast to the extremely polymorphic nature of the asymmetric form of St.B.U., the syndrome involving pterygium colli is so relatively uniform and characteristic that the diagnosis can ordinarily be accurately made on first examination. Essentially only three

other anomaly-complexes come into consideration in the clinical differential diagnosis, viz., mongolism, Klippel-Feil syndrome, and Status dysraphicus.

Transitional cases of *mongolism* may arise from the fact that in this disease there is usually a cutis laxa and a loose nape skin which occasionally even takes the form of a typical pterygium colli (Ullrich, 1930). Nevertheless, mongoloid idiocy is not only distinguished by a marked involvement of the internal organs but is also distinct in showing no sex preference. Clinically the differentiation will usually be possible from the fact that mongolism shows a highly characteristic behavior pattern with feeblemindedness, which is at least not obligatory in St.B.U.

Klippel-Feil syndrome presents a less clear basis for separation from both the phenogenetic and the clinical point of view. The distinction would, of course, be superfluous if a subcutaneous edema mechanism should prove responsible for this condition as well. On purely mechanical grounds one can well imagine a fusion of the cervical vertebral bodies in consequence of the pressure of a primary neck bleb. I regard this possibility, however, as unjustified. It is true that Klippel-Feil syndrome is not uncommonly accompanied by other anomalies similar to those found in St.B.U. (Rinvik, 1944). However, the central feature of Klippel-Feil syndrome is a localized developmental failure of the vertebrae, and this may occur in other cases in sections of the vertebral column other than the cervical region, in such a way that cerebrospinal blebs could not plausibly explain the state of affairs. Also, it must be noted that here again, as in mongolism, there is, to my knowledge, no marked predilection for the female sex.

It should be mentioned that Gilmour (1941) found *iniencephaly* more common in females than in males. This severe defect of the occipital region, which is incompatible with life, no doubt stands in close morphologic relationship with Klippel-Feil syndrome (Drachter, 1923). This is not to say, however, that it represents a specially severe manifestation of the same phenogenetic disturbance. Kaven (1943) also mentions that the female seems to be more severely affected in the case of the short-tailed anomaly of the house mouse, which is accompanied by blood blisters and vertebral deformities very similar to those in Klippel-Feil syndrome. All of these developmental anomalies of the axial skeleton are nevertheless far removed from the anomaly complex of *my* mice, and are presumably brought about through entirely different pathogenetic events. Finally, it may be mentioned that von Pfaundler's (1939) extensive studies on "Frühtod, Geschlechtsverhältnisse und Selektion" showed that developmental anomalies in general constitute almost the sole cause of intrauterine death for which there is a marked excess of female cases.

For genetic purposes, at any rate, it is advisable at present to separate Klippel-Feil syndrome from St.B.U. In general these two conditions are not difficult to distinguish clinically. Even without roentgenograms a synostosis of the vertebrae is usually apparent in these "hommes sans cou" by virtue of the reduced mobility of the neck, whereas in St.B.U. the head is freely mobile and the shortness of the neck is only an illusion due to the broad skin flaps. The broad neck in Klippel-Feil syndrome is admittedly not always due to lateral muscle-wings; there are sometimes "pure skin" folds of the sort seen in Turner's syndrome (Frawley, 1925; Martin, 1947). Although the low hair-line of the neck and the abnormal ears also agree with the features of St.B.U., cases with demonstrated vertebral changes should be separated from Turner's syndrome, rather than to designate such as combinations (Martin).

The greatest difficulties can arise in the clinical differentiation of St.B.U. and *Status dysraphicus*. Since the basis for the latter condition lies in a malformed defective closure of

the medulla which affects principally the dorsal marginal portions of the central canal throughout its length, there is no phenogenetic resemblance to St.B.U. Also, it is not possible to unify the two on the assumption that, in accordance with Bonnevie's view, cerebrospinal fluid may also escape from places other than the foramen anterius. All in all, the phenomenology of Status dysraphicus is not explicable on a subcutaneous edema mechanism. We are therefore faced only with a phenotypical overlapping of two syndromes, which, however, may be at times very extensive (Bremer, 1926; Passow, 1933). In individual cases a differential diagnosis may have to be based upon family studies. For example, I consider one of the families reported by Rossi and Howald (1947) in their paper on the genetics of St.B.U. to be an example of Status dysraphicus. The 18 year-old proposita with funnel chest shows a typical pterygium colli, but lacks infantile features, and the 2 brothers who show milder defects (funnel chest, clinodactyly) correspond much more closely with Status dysraphicus.

INHERITANCE

Up to the present time the available publications on the inheritance of St.B.U. have not taken account of the division which has now become apparent between the two phenogenetically distinct forms, nor have other confusing syndromes always been carefully excluded. For this reason the conclusion of Rossi and Howald (1947) that we are dealing with a facultative dominant gene cannot be definitely accepted. The first kindred adduced by these authors in evidence of the genetic pattern is, in all probability, an example of Status dysraphicus, as remarked above. In a second family, the proposita shows the typical symmetric syndrome with pterygium colli, while a paternal female half-cousin was said to show distinct signs of St.B.U. (lateral neck folds). Another pedigree previously reported by Rossi (1945) is concerned with a child with right-sided Pectoralis defect and "dorsal pads of the hands"; in the father polydactyly was present, and among the maternal relatives hypertelorism was found in several members belonging to three generations. The pedigree also shows a diabetic diathesis. This very cursory report may be retained for the genetic analysis of the asymmetric form of St.B.U., but the data should be restricted to the immediate sibship of the proposita.

Teveli (1930) recorded webbing of the third and fourth toes in the father of his patient. Ostertag and Spaich's report (1936) concerns a discordant pair of monozygotic twin brothers, one of whom showed the typical syndrome with pterygium colli and the other only *impressiones digitatae* and webbing of the second and third toes. Whether these minor anomalies, which are so frequent in the general population, can be regarded as "microforms" of the syndrome cannot be decided at present. In a brief discussion note, Baumann (1945) mentions three sibs who showed congenital lymphangiectatic edema, apparently without other anomalies. In a typical female case of pterygium colli, Cotterman (1948) found strabismus and epicanthus occurring as isolated anomalies in a brother, the mother, and a maternal cousin. Foucar (1948) cites the occurrence

of pterygium colli in two sisters described by Frawley (1925); these cases, however, are more probably Klippel-Feil syndrome.

This is all that is now available in the way of family reports. Obviously no clear evidence of inheritance can yet be claimed. Additional more extensive family studies are urgently needed, and these should not be difficult to obtain for the typical symmetric syndrome which includes pterygium colli. This easily recognized, and not exceptionally rare, complex is sufficiently homogeneous to serve well for such studies. For the typical or asymmetric form of St.B.U. the selection of propositi presents difficulties of a serious nature. However, since the purely *epigenetic process* of excessive exudation of cerebrospinal fluid is apparently responsible for these anomalies, the question of the mode of inheritance need not be posed in an overall sense.

For the symmetric form of St.B.U. or Turner's syndrome, a further investigation of the phenogenetic mechanism is also needed. We do not yet know in what way the symmetric accumulations of fluid arise in the integument. Also, the cause of the infantile dwarfness is not yet certain. An isolated impairment of the hypophysis through the pressure effect of a bleb derived from the neck region (Engel, 1940) seems highly improbable. As several authors have pointed out, the dwarfness of Turner's syndrome shows some distinct clinical differences from that of pituitary dwarfness (Schneider & McCullagh, Sharpey-Shafer, Greenblatt & Nieburgs, Flavell). Holmer (1948), as well as Schneider and McCullagh, assumes a primary disturbance of the gonads. In agreement with the increased urinary excretion of gonadotropic substances, a better therapeutic effect has been obtained with estrogenic hormones than with pure pituitary preparations. In histological studies of their patients, Atria and Donoso (1946) and Moss and Menk (1949) found the hypophyses essentially normal, whereas the ovaries showed regressive changes. Greenblatt and Nieburgs' male patient had a large penis and small testes, showing histologically a tubular hypoplasia with seemingly increased numbers of interstitial cells.

Neither a disturbance of the hypophysis or of the gonads, however, can serve as an adequate explanation of the syndrome in its entirety. The intimate interrelationships of these endocrine glands makes difficult an analysis of the exact nature of the endocrine disturbance, which must certainly play a part in this syndrome. However, endocrine disorders must, in any case, be of secondary significance in the phenogenesis of the syndrome as a whole. The beginning of the teratologic determination period must be placed at an early embryonic period; as yet there is no clear proof that ontogenetic events at this time may depend upon the endocrine system as in extrauterine life. It would not be contrary to this view, however, to suppose that some disturbance in the important organizer field of the mid-brain area might be responsible for the syndrome. It is very likely that other combinations of head and extremity anom-

alies—the so-called dyscranio-dysphalangias—may also be centrally controlled through disturbances in this region.

SUMMARY

The mechanism of wandering cerebrospinal fluid blebs discovered by Bonnevie in embryos of the Bagg-Little mouse mutant *my* ("myelencephalic blebs") may with full justification be applied to corresponding complexes of multiple anomalies in man.

By means of this theory a fully satisfactory explanation is afforded for the first time for nuclear lesions in the medullary portion of the brain-stem (nuclear aplasia) combined with (unilateral) Pectoralis defects and numerous associated deformities.

Since motor disturbances in the cranial nerve region and peripheral muscle defects are also observed in combination with lateral skin folds of the neck (pterygium colli) arising from congenital skin swellings (lymphangiectatic edema), it is natural to regard the various multiple anomalies accompanying pterygium colli as the equivalents of those present in *my* mice.

This complex of abnormalities described by me in 1930 has received increasing attention in the German-language literature under the designation of Status Bonnevie-Ullrich (St.B.U.). It is identical with a typical syndrome defined by Turner (1938).

From an analysis of all described cases it is evident that pterygium colli and its numerous allied anomalies is almost invariably associated with dwarfness and conspicuous infantilism in older female patients. The complex is strongly preferential for the female (4 ♀ : 1 ♂). This, plus the fact that there is a rather consistent symmetrical distribution of all of the defects, makes the syndrome incompatible with the wandering bleb mechanism. The latter leads one to anticipate a very polyphenic syndrome, with an asymmetric distribution of peripheral defects, like those found in typical (unilateral) St.B.U., as well as in the anomaly-complex of *my* mice.

In the symmetric form of St.B.U. one must think of an autochthonous origin of subcutaneous fluid accumulations which must account for the greater part of the abnormalities, just as in the typical or asymmetric conditions. The infantile dwarfness and the predilection for the female sex cannot be adequately explained at present.[5] The early teratogenetic time of determination, however, allows one to attribute at most a secondary significance to organ-controlled endocrine disturbances.

[5] Important in this regard is the demonstration of trophic pathways between the diencephalic sexual center and the sacral and lumbar centers. This nervous pathway, consisting of many neurones, apparently becomes united via the bundle of Schütz at the base of the rhomboidal sinus to the fasciculus parependymalis, which courses as a longitudinal tract through the substantia gelatinosa of the spinal cord (Krücke, 1949).

Since it appears necessary to modify the myelencephalic bleb theory for the symmetric form of St.B.U., which includes Turner's syndrome, and to postulate here a somewhat different edema mechanism, the two clinical pictures should be kept apart for purposes of genetic study. In this connection it is also necessary to differentiate the symmetric form from other syndromes having manifestations which sometimes overlap those of St.B.U. Difficulties in the differential diagnosis are especially furnished by some cases of Klippel-Feil syndrome and Bremer's Status dysraphicus.

REFERENCES

ABERLE-HORSTENEGG, W. 1937. *Zschr. Orthop.* 67: 21–29.

ALESSANDRI, H., ATRIA, A., & ZANARTU, J. 1945. *Rev. méd. Chile*, 73: 630–633.

ATRIA, R. A., & DONOSO, G. S. 1946. *Rev. méd. Chile*, 74: 491–496.

BAGG, H. J., & LITTLE, C. C. 1924. *Am. J. Anat.* 33: 119–145.

BAUMANN, T. 1945. *Ann. paediat.*, Basel, 165: 160.

BETTMANN, A. G. 1946. *Plastic & Reconstr. Surg.* 1: 205–215.

BIZZARRO, A. H. 1938. *Lancet*, Lond. 235: 828–829.

BLECHSCHMIDT, E. 1947. *Abh. Akad. Wiss. Göttingen;* 3. Folge, Heft 22.

BLECHSCHMIDT, E. 1948. *Mechanische Genwirkung*. Göttingen: K. G. Musterschmidt Verlag.

BONNEVIE, K. 1932. *Arch. Entwmech.* 126: 348–372.

BONNEVIE, K. 1934. *J. Exp. Zool.* 67: 443–520.

BONNEVIE, K. 1936. *Erbarzt*, 2: 145–150.

BONNEVIE, K. 1940. *Handbuch der Erbbiologie des Menschen, Bd. I.* Berlin: Springer.

BRAKHAGE, S. 1941. *Zschr. Kinderh.* 62: 686–690.

BREMER, F. W. 1926. *Deut. Zschr. Nervenh.* 95: 1–103.

BREMER, F. W. 1929. *Deut. Zschr. Nervenh.* 99: 104–123.

BUSSIÈRE, J. A. 1902. *Ann. hyg. méd. col.*, Par. 5: 686–688.

CAPURRO, A. M. 1941. *Dia. méd.*, B. Air. 13: 124–126.

CARPENTER, G. 1909. *Proc. R. Soc. M.*, Lond. 2: 45–199.

CHANDLER, F. A. 1937. *Am. J. Dis. Child.* 53: 798–803.

CLAUSEN, F. 1939. *Zschr. indukt. Abstamm.* 76: 14.

COTTERMAN, C. W. 1948. *Genetics*, 33: 607–608.

DE BRUIN, M. 1928. *Am. J. Dis. Child.* 36: 333–341.

DORFF, G. B., APPELMAN, D. H., & LIVESON, A. 1948. *Arch. Pediat.*, N. Y. 65: 555–561.

DRACHTER, R. 1923. *Klin. Wschr.* 2: 664.

DREYFUS, J. R. 1936. *Zschr. Kinderh.* 58: 165–177.

DUNN, L. C. 1934. *Proc. Nat. Acad. Sc. U. S.* 20: 230–232.

EBSTEIN, E. 1918. *Derm. Wschr.* 67: 607.

ENGEL, D. 1940. *Am. J. Dis. Child.* 60: 562–579.

ESSEN-MÖLLER. 1928. *Zschr. menschl. Vererb.* 14: 52.

FANCONI, G., & GROB, M. 1934. *Die klinische und forensische Bedeutung der Impressiones digitatae des Schädels. Zanggers Festschrift II.* Zürich: Rascher & Cie. p. 681.

FLAVELL, G. 1943. *Brit. J. Surg.* 31: 150–153.

FOUCAR, H. O. 1948. *Canad. M. Ass. J.* 59: 251–255.

FOURNIER, A., & HABART, A. 1948. *J. sc. méd. Lille*, 66: 270.

FRAWLEY, J. M. 1925. *Am. J. Dis. Child.* 29: 799–805.

FREEMAN, E. A., & SHELDON, J. H. 1938*a*. *Arch. Dis. Childh.*, Lond. 13: 277–283.

FREEMAN, E. A., & SHELDON, J. H. 1938*b*. *Proc. R. Soc. M.*, Lond. 31: 1116–1119.
FUNKE. 1902. *Deut. Zschr. Chir.* 63: 162–167.
GILMOUR, J. R. 1941. *J. Path. Bact.*, Lond. 53: 117–131.
GLANZMANN, E. 1946. *Die Einführung in die Kinderheilkunde, Bd. 2*, p. 172. Wien: Springer.
GREBE, H. 1944. *Zschr. menschl. Vererb.* 28: 209–261.
GREENBLATT, R. B., & NIEBURGS, A. E. 1948. *J. Clin. Endocr.* 8: 993–1003.
GROSS, M. 1939. *Mschr. Kinderh.* 78: 187–192.
GRUBER, G. B. 1934. *Beitr. path. Anat.* 93: 459–476.
GRÜNEBERG, H. 1943. *The Genetics of the Mouse.* Cambridge Univ. Press. xii + 412.
GRÜNEBERG, H. 1947. *Animal Genetics and Medicine.* New York, London: Hoeber. xii + 296.
GÜTERMANN, F. 1902. *Deut. Zschr. Nervenh.* 57: 203–226.
GUINAND-DONIOL, J. 1947. *Ann. paediat.*, Basel, 169: 317–324.
HAASE, L. 1942. *Veröff. Konst. Wehrpath.* 51:
HACKENBROCH, M. 1924. *Zschr. orthop. Chir.* 43: 508–524.
HAMNE, B. 1948. *Nord. med.* 38: 1135–1140.
HEIJBROEK, N. I. 1941. *Mschr. kindergeneesk.* 10: 267–276.
HEUBNER, O. 1900. *Charité Ann.*, Berl. 25:
HOFFMANN, H. 1937. *Arch. Kinderh.* 110: 1–24.
HOFMANN, A. 1925. *Arch. Kinderh.* 76: 285–287.
HOLMER, A. J. M. 1948. *Ned. tschr. geneesk.* 92: 1130–1134.
HUSLER, J. 1942. *Multiple Abartungen.* In Pfaundler-Schlossmann, Ergänzungswerk: *Handb. f. Kinderhk.* Berlin: Springer.
JACCOTTET, M. 1945. *Ann. paediatr.*, Basel, 165: 160.
KALDEBO, J. 1933. *Zbl. Chir.* 60: 2601–2603.
KAVEN, A. 1943. *Erbarzt*, 11: 49.
KIESER, W. 1939. *Zschr. menschl. Vererb.* 23: 594–619.
KOBYLINSKI, O. 1883. *Arch. Anthrop.*, Brnschw. 14: 343–348.
KOPITS, E. 1937. *Arch. orthop. Chir.* 37: 539–549.
KRÜCKE, W. 1949. *Deut. Zschr. Nervenh.* 160: 196–220.
LEOPOLD, J. S., & CASTROVINCI, F. 1934. *Arch. Pediat.*, N. Y. 51: 34–39.
LIEBENAM, E. 1938. *Zschr. menschl. Vererb.* 22: 373–417.
LITTLE, C. C., & MCPHETERS, B. W. 1932. *Genetics*, 17: 674–688.
MACCOLLUM, D. W. 1938. *N. England J. M.* 219: 251–254.
MARQUARDT, W. 1938. *Zschr. Orthop.* 67: 379–386.
MARTIN, C. A. 1947. *Laval méd.* 12: 461–475.
MASLOWSKI, H. 1928. *Mschr. Kinderh.* 40: 436–440.
MATOLCSY, T. 1936. *Arch. klin. Chir.* 185: 675–681.
MENZEL, W. 1939. *Zschr. klin. Med.* 135: 423–440.
MEYER, F. 1943. *Arch. Kinderh.* 129: 35–40.
MORANDO, G. C. 1948. *Pediatria*, (Riv.) 56: 746–752.
MOSEBACH, H. 1936. *Zschr. Orthop.* 65: 134–147.
MOSS, J. M., & MENK, K. F. 1949. *Virginia M. Month.* 76: 186–190.
NACHTSHEIM, H. 1943. *Jena. Zschr. Naturwiss.* 76: 81–108.
NAGEOTTE-WILBOUCHEWITCH, M. 1934. *Bull. Soc. pediat. Paris*, 32: 683–688.
NIEMEYER, M. L. 1946. *Zur Klinik der Arthrogryposis multiplex cong. bzw. den angeborenen Gelenkversteifungen mit Muskeldefekten.* Inaug. Diss. Göttingen.
NIEUWENHUIJSE, A. C. 1942. *Genetica*, Gravenh. 23: 289–299.
OSTERTAG, M., & SPAICH, D. 1936. *Deut. Zschr. Nervenh.* 141: 1–8.

PASSOW, A. 1933. *Arch. Augenh.* 107: 1–51.
PERITZ, R. 1912. *Nervenkrankheiten des Kindesalters.* Berlin: H. Kornfeld.
PETERSEN, G. A. 1939. *Zschr. Kinderh.* 61: 130–134.
PFAUNDLER, M. VON. 1939. *Zschr. Kinderh.* 60: 467–494.
PLAGENS, G. M. 1933. *J. Morph. Physiol.* 55: 151–183.
RANTASALO, V. 1936. *Acta paediatr.*, Upps. 18: 368–375.
RASPI, M. 1927. *Riv. clin. pediatr.* 25: 648–660.
RINVIK, R. 1944. *Acta paediatr.*, Upps. 31: 417–427.
ROSSI, E. 1945. *Helvet. paediat. acta*, 1: 134–146.
ROSSI, E., & HOWALD, E. 1947. *Helvet. paediat. acta*, 2: 98–102.
RUH, H. O., & DEMBO, L. H. 1927. *Am. J. Dis. Child.* 33: 249–258.
SCHADE, H. 1937. *Zschr. Morph. Anthrop.* 36: 375–381.
SCHMIDT, A. 1897. *Zschr. Nervenh.* 10: 400–409.
SCHNEIDER, R. W., & MCCULLAGH, E. P. 1943. *Cleveland Clin. Q.* 10: 112–125.
SCHÜSSLER, E., & LEISCHNER, A. 1944. *Zschr. menschl. Vererb.* 27: 745–758.
SCHWARTZER, K. 1938. *Mschr. Kinderh.* 76: 193–196.
SEHESTEDT, H. 1938. *Kinderärztl. Praxis*, 9: 56–59.
SHARPEY-SCHAFER, E. P. 1941. *Lancet*, Lond. 2: 559–560.
SHERESHEVSKI, N. A. 1925. *Vest. endokr.* no. 4.
SHERESHEVSKI, N. A. 1926. *Rev. fr. endocr.* no. 3.
SHERESHEVSKI, N. A. 1944. *Am. Rev. Soviet. M.* 1: 337–339.
SIEGMUND, H. 1938. *Zbl. allg. Path.* 70: 243.
SLONIMSKI. 1928. *Transactions de la Clinique neurologique de l'institut d'études médicales supérieures de Kiev*, 1: 173–213.
SPATZ, H., & ULLRICH, O. 1931. *Zschr. Kinderh.* 51: 579–597.
STECHE, 1905. *Deut. Zschr. Nervenh.* 28: 217.
STURKIE, R. D. 1941. *J. Morph.* 69: 517–535.
SYLVEST, O. 1940. *Ugeskr. laeger*, 102: 1270–1272.
TEVELI, L. 1930. *Orv. hetil.* 1: 92–94; Abst. in *Zbl. Haut. Geschlkr.* 34: 737.
TURNER, H. H. 1938. *Endocrinology*, 23: 566–574.
ULLRICH, O. 1930. *Zschr. Kinderh.* 49: 271–276.
ULLRICH, O. 1936. *Handb. Neurol.* 16: 139–181.
ULLRICH, O. 1938. *Klin. Wschr.* 17: 185–190.
ULLRICH, O. 1943. *Erg. inn. Med. Kinderh.* 63: 929–1000.
ULLRICH, O. 1943. *Zschr. menschl. Vererb.* 27: 651–681.
ULLRICH, O. 1944. *Antrittsvorles. der Rhein. Fried. Wilh. Univ., Bonn/Rhein.* 26: 1–19.
ULLRICH, O. 1949. *Erg. inn. Med. Kinderh.* (In press)
VERSCHUER, O. F., VON. 1940. *Anomalien der Körperform.* In Bauer-Fischer-Lenz, *Menschliche Erblehre und Rassenhygiene.* 5 Aufl., Band I, 2te Hälfte. *Erbpathologie.* München, Berlin: Lehmann.
VOLZ, H. 1938. *Zschr. Geburtsh.* 117: 131–147.
WAARDENBURG, P. J. 1934. *Klin. Mbl. Augenh.* 92: 29–44.
WEISSENBERG, S. 1928. *Anthrop. Anz.* 5: 141–144.
WERNHER, O. 1843. *Die angeborenen Zystenhygrome und die ihnen verwandten Geschwülste. Denkschrift.* Giessen.
WIETSCHKE, L. 1932. *Wien. klin. Wschr.* 1014–1015.
WITH, T. K. 1935. *Hospitalstidende*, 78: 556–560.

Unilateral Developmental Anomalies in Sisters
(Status Bonnevie-Ullrich)

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ULLRICH (1936) pointed out that certain congenital human anomalies of the head and extremities might find their embryological explanation in the damaging pressure action of wandering cerebrospinal fluid blebs, a mechanism shown by Bonnevie (1931, 1935) to be responsible for an inherited syndrome discovered in the house mouse by Bagg and Little (1924). Two principal anomaly complexes have thus come to be described under the title of "Status Bonnevie-Ullrich." One of these, which Ullrich believes to be attributable to an identical wandering bleb mechanism, consists of congenital nuclear defects (especially abducens and/or facialis paralysis), combined with various abnormalities—chiefly unilateral—of the ear, ocular adnexa, muscles (especially Pectoralis defect), and extremities (especially the hands). As Ullrich has remarked (1949), family studies are much needed, not only to decide whether these associated anomalies are hereditary, but also to gain further clues concerning the proposed theory of pathogenesis. To this end the authors wish to record some observations made very recently on a patient showing many of the aforementioned abnormalities.

CASE REPORT

D. C., a 9 year-old White female child (born August 28, 1940) was recently referred to the University Hospital (U.M.H. No. 664581) for surgical consideration with regard to a deviated nasal septum, malformed jaw, accessory auricular cartilages, and a "tumor of the left orbit." On the pedigree diagram (fig. 5) she is represented as *A-5*.

Birth and Developmental History. The patient was the product of a full term gestation and an apparently normal delivery. A deformity of the jaw, a malformed left ear, and an epibulbar tumor of the left eye were called to the mother's attention at the time of birth. There was reportedly no evidence of neonatal jaundice, anemia, or congenital edema. Development was slightly retarded. The child sat erect at 10 months and walked at the age of 14 months. She did not talk effectively until 5 years of age, and still has a nasal intonation and slight lisp. Measles and pertussis were experienced at 3 years and varicella at 3 years, 6 months, all without complications. The first grade of school was failed, and the child is regarded by her teachers as mentally retarded.

Physical examination. At 9 years, this girl is a well proportioned, but rather frail child, who is shy and frightened in public but is active and well adjusted in the home. Height 121.9 cm., weight 45.5 pounds. Except for the various anomalies of the head and face to be described, there are no grossly apparent defects. The neck, thorax, abdomen, genitalia and extremities are not abnormal, and the heart and lungs are normal to auscultation and per-

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cussion. Laboratory findings, consisting of urinalysis, Kahn sero-diagnostic reaction, and miniature chest film, were negative. The hemoglobin was 12.8 grams. The tuberculin skin reaction was negative (O.T. 1:10,000 I.D.).

Head and face. The skull appears somewhat smaller than average, but is symmetrical, except for some apparent flattening of the left mastoid eminence. The frontal bossae are rather prominent. There is marked facial asymmetry, due principally to an apparent shortening of the left half of the mandible, the symphysis being displaced about 1.5 cm. to the left (fig. 1). On palpation, the condylar portion of the left ramus appears to be missing or else there is a chronic luxation of the temporo-mandibular joint.

The left external ear is similar in size and shape to the normal right ear, but is situated about 1 cm. lower on the face (fig. 1). The auditory canal of the left ear is directed upwards, but is otherwise normal. The drum is intact. The left tragus is almost wholly missing, but there is a mound-shaped pretragal appendage, measuring about 1 cm. in diameter and projecting about 1 cm. away from the face (fig. 2). It appears to consist of one or more accessory cartilages. Between the rudimentary tragus and the appendage is a sinus or pit, and a smaller pit or dimple is situated behind the tragal remnant just within the external meatus. No drainage from these pits has been observed by the mother of the patient.

The nose is rather broad, with the tip bent slightly to the right. The nares are elliptical, the left being slightly larger than the right. The nasal septum is markedly deviated to the left anteriorly, with an apparent occlusion of the left passageway. The lips and oral cavity are normal except for a marked malocclusion of the teeth. There is a fibrous union of the central raphe, and palatal function is somewhat reduced on the left side. The left tonsillar fossa is higher than the right, and bulges forward. No difference is observed in the sizes of the tonsils.

Ocular examination. The two orbits appear equal in size and height, and their margins are normal and symmetrical to palpation. There are no gross defects of the lashes or lids, but the left palpebral fissure is somewhat narrowed, both vertically and horizontally. There is a ptosis of the left upper lid of approximately 1 mm., and a minimal epicanthus is present bilaterally. The left lacrimal caruncle is grossly absent, and a small symblepharon extends from the nasal third of the lower lid conjunctiva to the limbus at 8 o'clock. Also, in the left eye, a soft compressible yellowish fleshy mass measuring 7 x 4 mm. occupies the lateral bulbar conjunctiva and lateral inferior cul-de-sac. The tumor appears to be a dermolipoma; there are no included hairs or other unusual structures. It extends laterally and posteriorly over the surface of the globe into the deeper structures. Slit-lamp examination reveals that the growth has invaded the cornea to a depth of approximately 1 mm. at the 6 o'clock meridian. A well healed surgical scar is present on the surface of the tumor. A tumor of the left orbit was said to have been visible at birth and produced a slight bulging of the lower lid. Surgical excision was performed at the age of 15 months by Dr. D. F. DeForest of South Bend, Indiana, to whom we are indebted for the following details: "The tumor removed from the left bony orbit of *D. C.* was a dermoid cyst, approximately the size of a small hazel-nut attached to the periosteum. The fibrous wall was rather thick. The left lacrimal caruncle disclosed a congenital defect, as also did the left ear. The operation was limited entirely to the removal of the dermoid cyst."

In the primary position the eyes vary from straight to a few degrees of left hyperphoria, the latter being demonstrated only by the cover test. Extraocular muscle movements show a gross limitation of abduction in both eyes (paralysis of external recti) as well as an overshoot of the right eye and marked lag of the left eye on looking down to the left. There is also a moderate weakness of the internal recti, which is more marked in the left eye. The point of basal convergence is 75 mm. No weakness of the muscles of ex-

pression was demonstrated. Fig. 1 reveals a minor sagging of the left corner of the mouth, and this is more conspicuous in baby pictures, but appears to be the result of the reduced size of the mandible and maxilla on this side.

Examination by ophthalmoscope and slit-lamp microscope failed to disclose any abnormalities of the anterior ocular segment, optic media or fundus in either eye. The irides are hazel-brown, the left being somewhat darker than the right. The pupillary reflexes are prompt and equal bilaterally. The uncorrected visual acuity is 6/15 in each eye. The patient was refracted under cycloplegia and accepted the following correction: Right eye, +5.00 sph., +0.75 cyl., axis 75°; Left eye, +4.50 sph., +0.75 cyl., axis 115°. With correction the visual acuity is 6/12 − 3 in the right eye and 6/12 − 2 in the left eye. Color vision is normal (Ishihara).

Neurological examination. "The child was apprehensive and emotionally disturbed throughout the examination. There is a bilateral abducens paralysis. The tongue deviates markedly to the left when protruded, this being a result of the jaw deformity and deviation of the jaw to the left when opening the mouth. The superficial sensorium is intact. There is no motor weakness in any part of the body, no muscular atrophy, and no apparent ataxia. The gait and station are normal. The reflexes are normal, active and equal bilaterally. No Babinski sign is demonstrated. *Impression:* Probable congenital abducens paralysis, most likely a nuclear aplasia, in addition to other congenital deformities."

Audiometric findings were inconclusive due to poor cooperation at the time of examination. However, there appears to be no marked hearing defect in either ear.

Dermatological examination. The skin is normal in texture and pigmentation over the entire body surface, with the exception of certain nevi to be described. There is no suggestion of cutis laxa or pterygium colli. There are two interesting nevi of the form known as "leukoderma centrifugum acquisitum" (Sutton, 1916) or "halo nevus" (Feldman & Lashinsky, 1936). These are small pigmented papules surrounded by sharply delimited oval non-pigmented areas, resembling patches of vitiligo. The smaller nevus (1 x 2 cm.) is situated on the anterior abdomen, approximately on the left mammillary line at the level of the umbilicus; the larger one (2 x 3 cm.) is located on the medial aspect of the right thigh near the groin. In addition, a small (4 x 6 mm.) café-au-lait spot is present on the forehead near the midline, and a larger (1.5 x 3 cm.) triangular spot of the same kind is present on the chest 3 cm. below the left nipple.

Dermatoglyphic prints of the palms and fingers (tables 1, 2), as well as prints of the soles and toes, revealed no unusual pattern characteristics. The flexion creases of the palms are likewise normal. The nails show no abnormalities.

The eye-brows are symmetrical and of normal contour and pigmentation. The head hair is dark golden-brown, but numerous grey hairs are present in the central frontal ("widow's peak") region. These hairs do not form an albinoid streak or "white forelock," but are interspersed among pigmented hairs. The underlying skin in this area is pigmented and appears normal in all other respects. According to the mother, an abundance of grey hairs was first noticed in this region at the age of 2 years, but the greying seemed to diminish after the age of 5.

Roentgenological examinations. Films of the skull show no abnormality of the cranial vault except that it is relatively small for a patient of this age. The pituitary fossa is of normal size and contour. The left mastoid area is somewhat flattened and shows less pneumatization than does the right. The bones of the face are distorted, the mandible and maxilla being deflected to the left (fig. 3). There is some shortening of the horizontal ramus of the mandible and marked underdevelopment of the ascending ramus; the coronoid process is present, but is somewhat longer and thinner than usual, while the condyloid process is represented

by a short bony spur, the neck and condyle being absent. The condylar fossa on the left is somewhat shallow as compared to the right, presumably due to the absence of the condyle in the fossa. There is some associated distortion of the teeth, those in the left side of the

TABLE 1. PALM PATTERN FORMULAE
(Symbolism of Cummins & Midlo, 1943)
Main Lines D.C.B.A.T./Configurational Areas 1.2.3.4.5

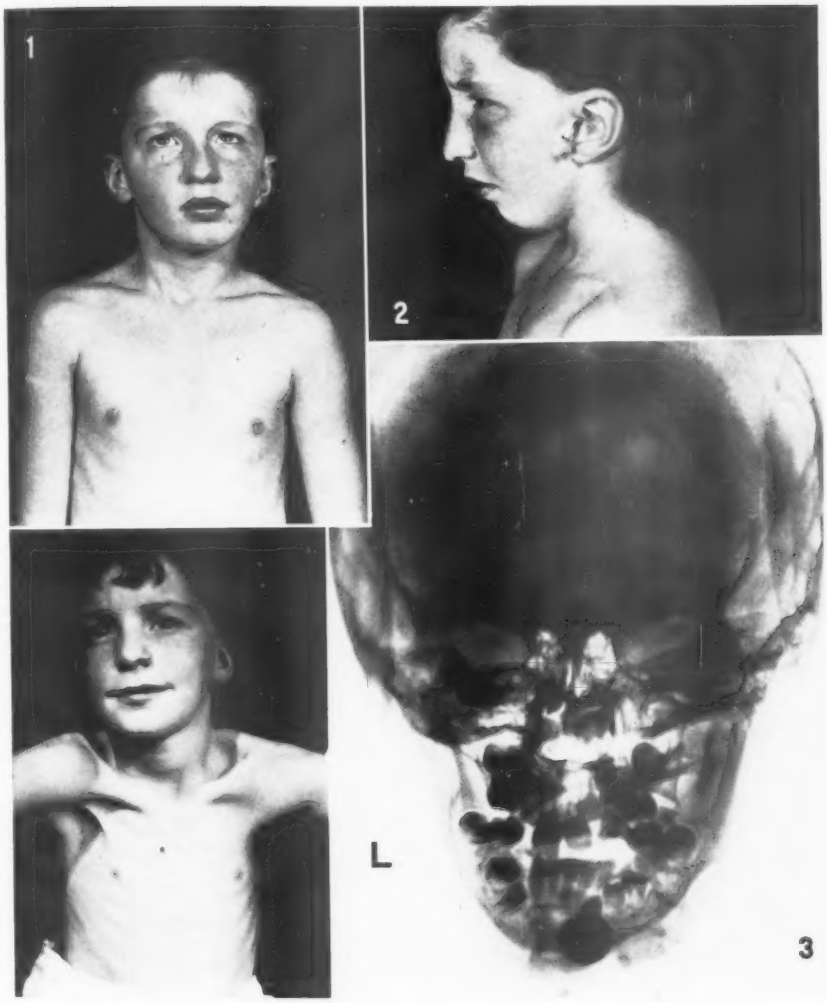
INDIVIDUAL	LEFT PALM	RIGHT PALM
C-1	10(11).*X*.5′(6).3-*t*-*L*^{r}.*O.O.O.V*	11(10).9.7/5′.3-*t*-*L*^{r}.*O.O.L.O*
A-1	9.*X*.5′.3-*t*-*L*^{r}.*O.O.O.V*	9(10).9.5′(6).3-*t*-*L*^{r}.*O.O.L.O*
A-2	11.*X*.7.3-*t*-*A*^{u}.*W*^{s}.*O.O.O*	11.10.8.3-*t*-*A*^{u}.*L*^{c}.*O.L.O*
A-3	11.*OidO*.4-*t*′-*O*/*A*^{c}.*O.O.O.O*	11.*OidO*.4-*t*′*t*-*A*^{u}/*V.O.O.O.O*
A-4	11.*X*.7.3-*t*-*V.V.O.V.O*	11.9.7.3-*t*-*L*^{r}.*O.O.L.O*
A-5	11/7.9.7.4-*t*′-*V*/*A*^{c}.*V.O.l.d.*	11.10.8.4-*t*′-*A*^{u}/*A*^{c}.*O.O.L.O*
A-6	10/7.9.7/5″.4-*t*-*L*^{r}.*O.V.l.d.*	11.9.7.4-*t*-*L*^{r}.*O.O.l.V*

TABLE 2. FINGER PATTERN TYPES AND RIDGE COUNTS
(Symbolism of Cummins & Midlo, 1943)

INDIVIDUAL	FINGERS LEFT HAND 5	4	3	2	1	FINGERS RIGHT HAND 1	2	3	4	5
C-1	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*A*^{t}	*L*^{u}	*L*^{u}	*L*^{u}
	0–8	0–12	0–12	0–8	0–11	18–0	0–0	11–0	10–0	9–0
A-1	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{r}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}
	0–8	0–12	0–11	9–0	0–15	17–0	2–0	13–0	7–0	7–0
A-2	*L*^{u}	*L*^{u}	*L*^{u}	*W*	*L*^{u}	*W*	*W*	*L*^{u}	*W*	*L*^{u}
	0–7	0–15	0–13	17–16	0–12	24–19	16–16	15–0	16–16	7–0
A-3	*L*^{u}	*W*	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*W*	*L*^{u}
	0–9	15–19	0–11	0–13	0–2	15–0	18–0	13–0	*–16	15–0
A-4	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*W*^{s}	*L*^{r}	*L*^{u}	*L*^{u}	*L*^{u}
	0–12	0–11	0–15	0–14	0–25	20–19	0–8	12–0	15–0	13–0
A-5	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{re}	*L*^{u}	*L*^{u}	*L*^{u}
	0–2	0–23	0–13	0–13	0–6	14–0	0–14	12–0	15–0	5–0
A-6	*L*^{u}	*L*^{u}	*L*^{u}	*L*^{u}	*W*^{s}	*L*^{u}	*L*^{u}	*L*^{u}	*W*	*L*^{u}
	0–10	0–12	0–12	0–12	5–15	24–0	14–0	17–0	18–11	15–0

* Ridge count indeterminate, due to aberrant ridge formation or scar.

mandible being smaller in all dimensions than those in the right, with their roots deflected laterally to an abnormal degree. The time schedule of dentition appears to be within normal limits, and the two halves of the maxilla and mandible are symmetrical with respect to the numbers of teeth developed and erupted. The maxilla is not decidedly abnormal; the nasal septum deviates moderately to the left. Contrary to the impression gained on physical



FIGS. 1, 2. Nine year-old proposita, *A-5;* facial asymmetry, malformed ear and jaw, and greying of hair in "widow's peak" area; combined with congenital abducens paralysis, absence of the left lacrimal caruncle, and other anomalies.

FIG. 3. Photoroentgenogram of *A-5;* hypoplasia of left mandible and maxilla, deviated nasal septum, and increased size of left orbital rim.

FIG. 4. (*lower left*, unlabeled) Seven year-old sister of the proposita, *A-6;* aplasia of the sternocostal part of the right Pectoralis major, hypoplasia (?) of the upper right part of Trapezius, reduced size of right nipple, and halo nevus of right chest.

examination, there is a distinct asymmetry in the sizes of the orbits as measured by the diameters of the orbital rims in anterior view: horizontal diam. right orbit 3.0 cm., left orbit 3.4 cm.; vertical diam. right orbit 3.7 cm., left orbit 4.0 cm.

Films of the spine show 13 thoracic vertebræ, the last segment supporting a well-developed thirteenth pair of ribs, measuring 5.4 cm. in length on the right and 5.2 cm. on the left. There are 6 lumbar vertebræ, with complete lumbarization of the first sacral segment. The seventh cervical vertebral body shows a distinct medial constriction or "butterfly deformity." In decreasing degree the same peculiarity is seen in the sixth and fifth cervical vertebræ and in the first five thoracic vertebræ. There is a distinct underdevelopment of the vertebral portion of the right first rib, producing a narrowed appearance as compared with its mate on the left. In addition, the second and third ribs on the right side are fused in the proximal fifths of their vertebral portions.

Films of the extremities show normal bone structure and relationships throughout. The sternum, clavicles and scapulæ are normal.

Course in Hospital. On September 27, 1949 plastic surgery of the face, with excision of the pre-auricular appendages was performed under ether anesthesia. The excised mass revealed a "large portion of cartilage, approximately 2.5 cm. in depth and approximately 1.5 cm. in

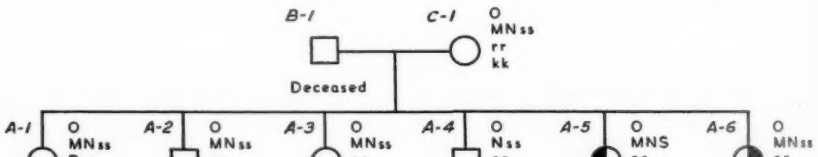


FIG. 5. Pedigree of University of Michigan Heredity Clinic Kindred No. 1693. S = presence ss = absence of agglutinogen *S* of Sanger and Race. kk = Kell-negative, Cellano-positive. For the antisera used in determining these two antigenic systems, the authors are greatly indebted to Dr. R. R. Race and Dr. Philip Levine.

width. The cartilage was well adhered to the surrounding structures, and no nerves or vessels were destroyed in the process to the knowledge of the operator."

Family History. The parents of this patient are not known to be related; the child's 8 great-grandparents bear different family names, so that any parental consanguinity must, in all probability, be more remote than second cousin relationship. The patient's father (*B-1*), a construction worker, died at age 52, two years previous to our investigation, the result of a 5-story fall. He was described as showing none of the abnormalities present in *A-5*. A summary of the abnormalities found in the mother and 5 sibs of the patient follows:

C-1, the 39 year-old mother of the patient (born Feb. 5, 1911) is a short, stocky woman, showing no distinct facial asymmetry, no apparent deformities of the limbs, muscular defects, cranial nerve deficiencies, or significant ocular findings. Her six living children (fig. 5) represent her total number of pregnancies, there being no miscarriages, stillbirths or children dying in infancy. All of her pregnancies were of normal duration and delivery was uneventful in each case except for *A-2* and *A-6*; the latter were each born 2 weeks prematurely and labor was medically induced. There is no history of exanthematous or febrile disease in any pregnancy. She has never received a transfusion of blood or plasma. Two years before

the birth of her first child her back was injured in an auto accident. In the fourth month of the fifth pregnancy the back was again injured in a fall, and a second auto accident occurred during the sixth pregnancy, but there were no physical injuries.

A-1, *A-2*, *A-3*, and *A-4*, the four older sibs of the proposita, were found to possess none of the abnormalities listed below for *A-5* and *A-6*. A few minor abnormalities were noted: a prominent Darwinian tubercle of the right ear is present in *A-1* and *A-3*, the right great toe of *A-1* appears somewhat shorter than the corresponding toe on the left foot, and a mild camptodactyly of the little finger is present bilaterally in *A-1*. Ocular examinations of the four children revealed no significant defects. No X-ray studies have as yet been made on *A-1*, *A-2* or *A-3*. In the brother, *A-4*, there is a history of retarded cranial ossification with several epileptiform seizures in infancy. Also, as a result of a hit by an automobile at age 6, he suffered a "concussion of the brain," fractures of the right leg, and injury to the back. There are scars over the knees and a scar over the lower lumbar region. X-ray films show no defects of the cranium or facial bones at the present time. Also, films of the spine show no abnormalities. Mentally, as well as physically, this boy appears to be quite normal.

The dates of birth of the older sibs are as follows: *A-1*, October 24, 1930; *A-2*, November 21, 1931; *A-3*, August 26, 1935; *A-4*, April 6, 1938.

A-6, the 7 year-old sister of the patient, born July 18, 1942, is a thin, somewhat poorly nourished child; height 119.1 cm., weight 43 pounds. The dental hygiene is very poor, the anterior upper teeth are missing, and there is a mild speech disability affecting primarily the enunciation of the letter *s*. The head is symmetrical and exhibits none of the abnormalities seen in *A-5*. The eyelids are normal, with the exception of a minimal degree of epicanthus bilaterally. The irides are hazel brown. The eyes are straight in the primary position. Extraocular muscle movements are normal, except for a marked overshoot of the right eye on downward-leftward gaze. The external and internal ocular examination revealed nothing of significance. The extremities are normal. In infancy, a slight abduction defect of the right foot was noticed by the mother, but there is no evidence of such at present. The abdomen, pelvis, genitalia and extremities are grossly normal and symmetrical.

There is a conspicuous defect of the Pectoralis major on the right side (fig. 4). The entire sternocostal portion of the muscle is apparently missing, but the clavicular portion seems to be present and is perhaps somewhat overdeveloped, which probably accounts for a fair strength in abduction and internal rotation of the right arm. There also appears to be some degree of underdevelopment of the upper part of the Trapezius on the right side. The skin over the right chest appears normal, except for a halo nevus situated over the right second sternocostal articulation. The right nipple is normal in structure, but the areola is smaller (7 x 10 mm.) than that of the left nipple (9 x 12 mm.). Tactile sensation is not impaired in the skin over the defective pectoral muscle, and skin conductivity tests show undiminished sweat excretion on this side of the chest.

Neurological examination disclosed no signs of cranial nerve deficiencies, and the sensory and motor development was normal throughout. Reflexes are normally active and equal bilaterally. Except for the small halo nevus of the chest, there are no apparent abnormalities of the skin, hair, teeth or nails.

Roentgenograms of the head show prominence of the distal markings on the inner table of the calvarium, but there is no other sign of increased intracranial pressure and this finding of itself is insufficient for such a diagnosis. There is no evidence of abnormal intracranial calcification. The bones of the face show no unusual asymmetries.

Films of the chest show no abnormalities of the heart or lungs. There are no apparent defects of the sternum or ribs, but there is a slight reduction in size of the right hemithorax

as compared with the left, with a definite increase in radiolucency on the right side, which is compatible with the clinical diagnosis of Pectoralis defect.

Films of the spine show no defects of the ribs or vertebræ like those seen in *A-5*; only eleven pairs of ribs are developed.

DISCUSSION

Summarizing, the following anomalies were observed in the 9 year-old proposita of the family:

1. Bilateral ophthalmoplegia (abducens defect);
2. Hypoplasia of the body and ramus of the left half of the mandible, with reduction in size of teeth;
3. Malformed left ear, with pretragal appendage;
4. Flattening of left mastoid prominence;
5. Deviated nasal septum, with subtotal occlusion of the left airway;
6. Aplasia of the left lacrimal caruncle, with symblepharon;
7. Epibulbar tumor (dermolipoma) of left eye;
8. Enlargement of left orbital rim;
9. Greying in infancy of the head hair in the central frontal area;
10. Halo nevi (leukoderma centrifugum acquisitum) of left abdomen and right thigh;
11. Hypoplasia of vertebral portion of right first rib;
12. Synostosis of the necks of the right second and third ribs;
13. "Butterfly deformity" of 7th cervical and adjacent vertebral bodies;
14. Supernumerary (thirteenth) thoracic vertebra, with well developed ribs;
15. Supernumerary (sixth) lumbar vertebra.

In the 7 year-old sister, we observed:

1. Aplasia of the sternocostal portion of the right Pectoralis major, with reduced size of right nipple;
2. Halo nevus of right anterior chest.

Associated with congenital abducens paralysis, we thus find unilateral anomalies of the ear, ocular adnexa and other facial structures which have been defined as a special anomaly-complex or syndrome. An additional developmental error, also emphasized by Ullrich as a common feature of the typical syndrome, namely unilateral Pectoralis defect, was encountered, not in combination with the above, but occurring in a sister. These correlations would seem to strengthen the supposition that the various anomalies actually do comprise a syndrome and that this may be hereditary in origin.[1]

With respect to the possibility that wandering blebs of cerebrospinal fluid may determine the various defects, we do not feel that our observations detract in any way from this possibility, unless the various irregularities of the verte-

[1] Other recent authors have commented on the frequent association of unilateral Pectoralis defect with syndactyly, polydactyly and atrichosis of the homolateral hand, as well as aplasias of the adjacent mammary gland and ribs (Lemos Torres, 1947; Soderburg, 1949).

bral column seen in *A-5* must be accounted for on the same basis. On the other hand, it is possible that these are unrelated in etiology to those of the head region. We hope later to obtain roentgenograms of the spines of the mother and sibs, which may possibly throw some light on this problem.

In addition to the similarities pointed out by Ullrich (1949), our case presents certain other malformations bearing a resemblance to the anomalies of "myelencephalic bleb" mice. Defects of the jaw, varying from complete agnathia to slight reduction of one half of the mandible with a resulting lateral deviation of the snout, were sometimes present in mice showing defects of the eyes and eyelids. As would be expected on Bonnevie's analysis, the underdeveloped half of the jaw always occurred on the side of the affected eye (Johnson, 1934).

The localized greying of the head hair in our patient might also be compared with the defective hair development recorded by Bagg and Little (1924) and others. Over the backs of the animals there sometimes occurred areas in which the hair was short and deficient in pigment, such areas being shown by Bonnevie (1934) to be the tracks over which blebs had migrated, causing a splitting of the embryonic epidermis and corium, which subsequently reunited as the bleb moved on to a more stable position. This disruption in the development of hair follicles results in a defective hair growth which characteristically is evident only in the juvenile coat of the animal, normal fur eventually taking its place. In this latter respect, the observation by our patient's mother that the spot of greying has tended to diminish since age 5 is interesting.

It is, of course, possible that the "halo nevi" seen in *A-5* and *A-6* do not constitute a part of the syndrome, irrespective of the mechanism which may be responsible for the latter. They were, however, found only in these two members of the family. In *A-6* the nevus borders on the area of the defective pectoral muscle. It may also be mentioned that Niles (1941) suspects that the lesions of "leukoderma centrifugum acquisitum" are congenital but transitory nevi, since they appear to have been observed only in children.

Among the various defects of the ocular adnexa found in cases of Status Bonnevie-Ullrich, benign tumors, in the form of dermoid cysts or dermolipomas, have not, to our knowledge, been previously mentioned. It would perhaps not be unreasonable to expect such "developmental arrests" in consequence of the disturbances produced by cerebrospinal fluid blebs. At the same time, it does not seem to us likely that the presence of a tumor could in itself have accounted during embryogenesis for the other anomalies in our patient. Whatever may be the explanation for their association in this case, it seems probable that the majority of such tumors have a different etiology. There is little to suggest that they may be hereditary, although Sæbø (1948) observed a conjunctival dermolipoma of the right eye in a girl, the girl's mother, and the maternal grandfather.

No abnormalities of the hands or feet are present in *A-5* or *A-6*. On the bleb

hypothesis one would therefore assume that the primary neck blebs localized on the left side of the head (in *A-5*) or on right side of the thorax (in *A-6*), but did not migrate into the limb buds, or at least not in sufficient quantity to produce marked deformities. In Bagg and Little's original strain of myelencephalic bleb mice the anomalies were not infrequently confined to the head region. Moreover, through selective breeding, substrains were obtained in which only head defects were found, due presumably to the concentration of modifying genes which somehow reduced the probability of blebs migrating into the trunk region (Little & McPheters, 1932).

Although palm and sole prints revealed no unusual configurations in *A-5* or *A-6* (tables 1, 2), we feel that dermatoglyphs—especially of the palms—might be studied with profit in all cases of Status Bonnevie-Ullrich. It is known that characteristic alterations of the friction ridge patterns may occur even in the absence of gross skeletal derangements, as in minor zygodactyly (Cummins & Midlo, 1943) and in mongoloid idiocy (Cummins, 1939). It therefore seems likely that edema of the fetal extremities due to terminalized blebs might in some cases produce dermatoglyphic changes unaccompanied by other observable effects.

It should perhaps not be left unmentioned that the mother of our patient considered that the injuries sustained in her last two pregnancies may have been responsible for the abnormalities of her two daughters. Also, it may not be without significance that the two affected children are the *last-born* in the sibship. In general, the possible effects of birth order and maternal age deserve investigation for both the symmetrical and asymmetrical forms of St. B.U. as defined by Ullrich (1949). Wiener (1947) has postulated that agglutinative thrombi resulting from the action of anti-Rh or other maternal isoagglutinins might lodge in embryonic blood vessels, producing various developmental anomalies. If such a process occurs, we would anticipate defects of a rather nondescript nature and of chiefly unilateral distribution, like those characterizing St.B.U., with the additional peculiarity that later-born children would show the defects with higher probability and that symptoms of hemolytic disease might be common in such patients and in their sibs. In the present family the mother was found to be Rh-negative, but all of her children, excepting the first, were also Rh-negative (fig. 5). Of the other blood factors tested, only the *S* factor of Sanger and Race showed an incompatible arrangement in mother and child (*A-5*). Tests of the mother's serum, in varying dilutions, against saline and serum-suspended cells of each of her children failed to disclose any irregular agglutinins. Also, as previously mentioned, the mother denied the occurrence of miscarriages, stillbirths, or symptoms of hemolytic disease in her children.

SUMMARY

A sibship of 6 children is described in which 2 sisters show various unilateral developmental anomalies (Status Bonnevie-Ullrich). The 9 year-old proposita

shows bilateral abducens paralysis, combined with a left-sided deformity of the ear, nose and mandible, absence of the lacrimal caruncle, benign tumors of the ocular adnexa, and other defects. A 7 year-old sister was found to possess right-sided Pectoralis defect, with hypoplasia of the right nipple. These cases are briefly discussed from the standpoint of Ullrich's (1936) theory, which postulates that the syndrome may be a homolog of the "myelencephalic bleb" complex in the house mouse.

REFERENCES

BAGG, H. J., & LITTLE, C. C. 1924. Hereditary structural defects in the descendants of mice exposed to Roentgen ray irradiation. *Am. J. Anat.* 33: 119–145.

BONNEVIE, K. 1931. Vererbbarer Cerebrospinaldefekt (?) bei Mäusen mit sekundären Augen- und Fussanomalien nebst Turmschädelanlage. *Ske. Norske Vidensk. Akad.*, Oslo, 1930, No. 13, pp. 26.

BONNEVIE, K. 1934. Embryological analysis of gene manifestation in Little and Bagg's abnormal mouse tribe. *J. Exp. Zool.* 67: 443–520.

BONNEVIE, K. 1935. Vererbbare Missbildungen und Bewegungsstörungen auf embryonale Gehirnanomalien zurückführbar. *Erbarzt*, 2: 145–150.

CUMMINS, H. 1939. Dermatoglyphic stigmata in mongoloid imbeciles. *Anat. Rec.* 73: 407–415.

CUMMINS, H., & MIDLO, C. 1943. *Finger Prints, Palms and Soles.* Philadelphia: Blakiston Co. pp. xi, 309.

FELDMAN, S., & LASHINSKY, I. M. 1936. Halo nevus. *Arch. Derm. Syph.*, Chic. 34: 590–604.

JOHNSON, P. L. 1926. An anatomical study of abnormal jaws in the progeny of X-rayed mice. *Am. J. Anat.* 38: 281–308.

LEMOS TORRES, U. 1947. Aplasia dos músculos peitorais. *Rev. med. cir. S. Paulo*, 7: 187–197.

LITTLE, C. C., & MCPHETERS, B. W. 1932. Further studies on the genetics of abnormalities appearing in the descendants of X-rayed mice. *Genetics*, 17: 674–688.

NILES, H. D. 1941. Leukoderma centrifugum acquisitum. *Arch. Derm. Syph.*, Chic. 43: 357–360.

SÆBØ, J. 1948. Lipoma conjunctivae in three generations. *Acta ophth.*, Kbh. 26: 447–450.

SODERBERG, B. N. 1949. Congenital absence of the pectoral muscle and syndactylism; a deformity association sometimes overlooked. *Plastic & Reconstr. Surg.* 4: 434–438.

SUTTON, R. L. 1916. An unusual variety of vitiligo (Leukoderma centrifugum acquisitum). *J. Cutan. Dis.* 34: 797–800.

ULLRICH, O. 1936. Angeborene Muskeldefekte und angeborene Beweglichkeitsstörungen im Gehirnnervenbereich. *Bumke-Förster Handbuch der Neurologie*, vol. 16, pp. 139–181. Berlin: Springer Verlag.

ULLRICH, O. 1949. Turner's syndrome and Status Bonnevie-Ullrich. *Am. J. Human Genet.* 1: 179–202.

WIENER, A. S. 1947. Pathogenesis of spina bifida and related congenital malformations. *N. Y. State J. M.* 47: 985–988.

SHORT PAPERS AND REVIEWS

Note on the Genetics of Acrokeratosis verruciformis (Hopf)

ACROKERATOSIS verruciformis is a nevoid dermatosis characterized by verrucoid, lichenoid, polygonal papules found on the dorsa of the hands and feet, with some involvement of the palms, flexor surfaces of the fingers, wrists, and forearms. The individual lesions are round, polygonal or oval, keratotic papules, varying in size from about 1 to 3 mm. in diameter, raised about 0.5 to 1 mm. above the level of the skin. They vary in color from that of the normal skin to a reddish brown, and are of firm consistency.

The histological changes as described by Hopf (1931) in his original presentation of two cases differentiates this condition from others which it may simulate clinically. The essential picture is: mild to moderate acanthosis, a circumscribed hyperkeratosis with invagination of the corneum, corresponding to the rete pegs which form a wavy line. There is an increase in the granular layer, but no vacuolation, parakeratosis, or cellular degeneration. The corium is essentially normal.

While there have been a number of individual case reports of this entity, a review of the literature reveals only a few references to its familial incidence. In a second paper on this entity, Hopf (1933) cites Rehn as describing the condition in a 28 year-old woman whose mother and two brothers had similar lesions. Danbolt (1935) presented four cases in three generations of a family; the 21 year-old patient, his mother, his maternal grandfather and the sister of the grandfather. Kovacs' case report (1940) mentioned involvement of the father and one sister of his 77 year-old female patient, but not of her mother or two other sibs. One of us (A. B. Loveman) and Graham (1941) reported the occurrence of this condition in a 21 year-old woman and her mother, but not in her only child, who was then 3 months old. However, eight years after the original report, this same child now shows well developed lesions of acrokeratosis verruciformis. The most extensive report of the familial incidence of this condition is by Niedelman (1947), wherein he presents four generations of a family showing 4 affected males, 10 affected females, 3 unaffected males, and 3 unaffected females.

In our family we could find no evidence of parental consanguinity in the 3 affected sibships. Also, there were no cases of epilepsy. However, the three individuals seen by us demonstrated definitely borderline grades of intelligence. Niedelman reports similar findings in his family, although the other authors do not specifically mention such factors in their papers.

From the available data it appears that acrokeratosis verruciformis, as is

the case with many other nevoid conditions, is inherited as a regular, autosomal, Mendelian dominant characteristic.

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REFERENCES

DANBOLT, N. 1935. Darier's sygdom kombinert med disseminat keratodermi pa hender og fotter (Acrokeratosis verruciformis Hopf) og keratoma dissipatum (Brauer) i familaer optreden i 3 generasjoner. *Norsk. mag. laegevid.* 96: 246–258.

HOPF, G. 1931. Ueber eine bisher nicht beschriebene disseminierte Keratose (Akrokeratosis verruciformis). *Derm. Zschr.* 60: 227–250.

HOPF, G. 1933. Morphologische und pathogenetische Untersuchungen über primäre Keratosen. *Arch. Derm. Syph.*, Berl. 167: 344–376.

KOVACS, S. 1940. Ein Fall von Akrokeratosis verruciformis Hopf. *Dermatologica*, Basel, 81: 6–11.

LOVEMAN, A. B., & GRAHAM, P. V. 1941. Acrokeratosis verruciformis (Hopf). *Arch. Derm. Syph.*, Chic. 43: 971–979.

NIEDELMAN, M. L. 1947. Acrokeratosis verruciformis (Hopf). *Arch. Derm. Syph.*, Chic. 56: 48–63.

Rh Nomenclature

CONSIDERABLE confusion exists as to the nature of the contribution made by Fisher to the field of the Rhesus blood factors— and because of this the following analysis has been prepared. Actually, Fisher's contribution can be divided into three distinct parts, namely, 1) his prediction of the existence of more than one Hr factor, 2) the theory of triple linked genes, and 3) the C-D-E nomenclature of Fisher, Race and Cappell.

1) Following the demonstration of the three Rh factors, Rh_0, rh′, and rh″ by Wiener (1943*a*, *b*) and of the first Hr factor, hr′, by Levine (1943) and by Race and coworkers (1943, 1944), Fisher (1944) made the brilliant suggestion that two more Hr factors might exist, these being reciprocally related to Rh_0 and rh″ just as hr′ is reciprocally related to rh′. Mourant (1945) found an example of anti-hr″ and recently another such serum has been found by Wiener and Peters (1948), while Haberman, Hill, Everist and Davenport (1948) found two examples of anti-Hr_0. Thus, Fisher's prediction has been fulfilled and its correctness is universally acknowledged.

2) The theory of linked genes, as contrasted with multiple alleles, is not original with Fisher, because it had been considered previously by Wiener (1943*c*) and was disproved and discarded at a time when only Rh_0 and rh′ were known. At that time these antigens were designated as Rh_1 and Rh_2 respectively. Since this work appears to have been overlooked it is quoted in its entirety from the 1943 edition of Dr. Wiener's book.

"The reactions could be explained most simply by assuming the existence of two qualitatively different agglutinogens, Rh_1 and Rh_2 in the blood cells, corresponding to the agglutinins anti-Rh_1 and anti-Rh_2. The four sorts of blood would then have the compositions Rh_1Rh_2, Rh_1, Rh_2, Rh-negative, respectively. This assumption would imply the existence, however, of two corresponding genes *Rh*$_1$ and *Rh*$_2$, which would have to be either independent, linked, or allelic. The first two possibilities are excluded since the product of the frequencies $Rh_1Rh_2 \times$ Rh-negative is much greater than $Rh_1 \times Rh_2$. Moreover, the existence of allelic genes *Rh*$_1$ and *Rh*$_2$ in individuals whose blood reacts with both anti-Rh_1 and anti-Rh_2 would necessitate that this class not exceed 50 per cent, while the actual frequency is 70 per cent. Accordingly, the observations are best explained by assuming the existence of 3 qualitatively different Rh agglutinogens instead of only 2, one type reacting with anti-Rh_1 serum but not anti-Rh_2, a second reacting with Rh_2 but not with anti-Rh_1, and a third reacting with both sorts of sera."

The calculations have recently been confirmed by Rife (1948) who extended them to include all three Rh factors and all three Hr factors. Moreover, the family and statistical studies of Wiener and co-workers (1947), Race and co-workers (1944), and others fully support the theory of multiple alleles, while there is no tangible evidence to support the theory of linked genes.

3) The introduction of a duplicate set of notations involving the letters C-D-E was an unfortunate development. To use two names when one is sufficiently explicit contributes confusion rather than clarity. The Rh factor gets its name because of the work of the discoverers, Landsteiner and Wiener who produced the first anti-Rh sera by immunizing animals with the blood of Rhesus monkeys. When the existence of two additional Rh antigens was later demonstrated, the designations rh′ and rh″ were invented for them to show their relationship to the original and most important antigen, Rh_0. The designations C-D-E are misleading because they incorrectly imply a relation to the A-B antigens, and some of the letters have already been used for other human blood factors so that ambiguity results. Moreover, there is no method of distinguishing the most important antigen, Rh_0, from the others. Numerous other disadvantages of the C-D-E notations have been pointed out by Wiener (1946*a*, *b*; 1948*a*, *b*), of which may be mentioned especially their lack of priority.

The symbol Hr was introduced by Levine (1943) to indicate the reciprocal relation of this factor to Rh. Accordingly, when Fisher's prediction proved to be correct, the symbols hr″ and Hr_0 were already waiting, so that the assertion that the symbols e and d have priority is based on misconception.

As an example of the misunderstanding which prevails, the following statement from a recent paper by Race, Sanger and Lawler (1948) is quoted: "The triple allelomorphic nature of the Rh antigens, discovered by Fisher, is now universally accepted as an established fact. . . . At first the theory was actively opposed by Wiener. After Mourant's discovery of anti-e serum and the consequent establishment of the existence of e, Wiener accepted Fisher's

theory by the translation of anti-e into anti-hr″ and anti-d into anti-Hr_0, but has since disputed it again." In the first sentence the universal acceptance of Fisher's prediction of three Hr factors (discussed under 1 above) has been confused with the theory of triple linked genes (discussed under 2 above). While Wiener was skeptical about the *prediction* at first, he now accepts it. However, as far as I know, Wiener never changed his mind about the *genetic theory* as Race implies, because in this he anticipated Fisher (as explained under 2).

It seems appropriate to point out also the feebleness of the argument recently put forward by Mourant (1948) in support of the British C-D-E notations as against the International Rh-Hr Nomenclature. He writes: "It should also be pointed out that Wiener's present nomenclature differs greatly from that originally put forward, and a claim for priority for can scarcely be based on the fact that his original system was published before that of Fisher." It is absurd to argue that modifications introduced to keep pace with the progress of knowledge and understanding affect the priority of any discovery. Even the C-D-E nomenclature has been revised several times to take new findings into account.

With regard to the remark by Mourant concerning the "obvious advantage" of Fisher's notation, this has no place in scientific discussions, since the word "obvious" as used is an appeal to emotion rather than to reason. If there really were any advantages to the C-D-E notations they could be listed.

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REFERENCES

Fisher, R. A. Cited by Race, R. R. 1944. *Nature*, Lond. 153: 771–772.
Haberman, S., Hill, J. M., Everist, B. W., & Davenport, J. W. 1948. *Blood*, Balt. 3: 682–688.
Levine, P. 1943. *J. Pediat.*, S. Louis, 23: 656–675.
Mourant, A. E. 1945. *Nature*, Lond. 155: 542.
Mourant, A. E. 1948. *Nature*, Lond. 161: 492.
Race, R. R., Sanger, R., & Lawler, S. D. 1948. *Ann. Eugen.*, Cambr. 14: 171–184.
Race, R. R., & Taylor, G. L. 1943. *Nature*, Lond. 152: 300.
Race, R. R., Taylor, G. L., Ikin, E. W., & Prior, A. E. 1944. *Ann. Eugen.*, Cambr. 12: 206–210.
Rife, D. C. 1948. *Ohio J. Sc.* 48: 116–118.
Wiener, A. S. 1943*a*. *Proc. Soc. Exp. Biol.*, N. Y. 54: 316–319.
Wiener, A. S. 1943*b*. *Science*, 98: 182–184.
Wiener, A. S. 1943*c*. *Blood Groups and Transfusion*. 3rd Edition. Springfield, Illinois: C. C. Thomas. p. 254.

WIENER, A. S. 1946*a*. *Brit. M. J.* 1: 982–984.
WIENER, A. S. 1946*b*. *Science*, 104: 578–579.
WIENER, A. S. 1948*a*. *Lancet*, Lond. 1: 343.
WIENER, A. S. 1948*b*. *Brit. M. J.* 1: 305; and 1: 404.
WIENER, A. S., & PETERS, H. R. 1948. *Am. J. Clin. Path.* 18: 533–536.
WIENER, A. S., SONN-GORDON, E. B., & HANDMAN, L. 1947. *J. Immun.*, Balt. 57: 203–210.

Pedigrees of Negro Families

By R. RUGGLES GATES (Biological Laboratories, Harvard University, Cambridge 38, Mass.). Philadelphia: The Blakiston Company, 1949. Pp. viii, 267; frontispiece +245 figures. $5.50.

SOME two hundred pedigrees of "Negro families" are assembled and analyzed in this book. Most of the pedigrees were compiled by the author's students, who had traced specific traits in their own families or in families well known to them. The majority of the families are in the United States, the remainder being in Canada, the West Indies and British Guiana. The traits represent a large range of diverse abnormal and normal conditions; in all, 54 traits are listed in the table of contents.

Some pedigrees have been used for more than one trait. The numbers of pedigrees representing the various traits are widely variable, ranging from none to several or even many. A page and a third of text, devoted to a general description of mongolian idiocy, lacks any reference to the family of the one case examined. Two traits, polydactyly and skin color, are here selected for comment because of their special interest.

Twenty-seven pedigrees of polydactyly are presented. Each is charted and some of the pedigrees are discussed in detail. All affected individuals have supernumerary little fingers that vary in degree of development. Some cases present also a supernumerary little toe, these occurring usually in association with the more fully developed postminimi of the hands. In 22 pedigrees there is dominant inheritance. In the sibships where one parent is presumably heterozygous for polydactyly there are 178 affected individuals and 174 unaffected. The sex distribution in the total affected is 122 males and 80 females. Five pedigrees, with a total of 13 affected and 27 normal sibs, are interpreted as probable recessive inheritance—though with recognition of the possibility that such pedigrees may be explained on the basis of low penetrance of a dominant gene. The observation that polydactyly is at least characteristically dominant in Negroes is stressed as an indication against the view that Negroes are distinguished, as compared with Whites, by recessive inheritance of this anomaly. The question is raised as to whether the degrees of structural expression of polydactyly are conditioned by different genes, and answered with the conclusion that the facts are against this assumption. It is emphasized that the dominant and recessive pedigrees do not differ with respect to degrees of digital development; in dominant pedigrees polydactyly is no more fully expressed anatomically when the affected person is homozygous.

In the discussion of skin color there are presented 11 pedigrees that illustrate crossing of the Negro with another race, usually White. Evidence is presented to show that in the racial crosses skin color segregates independently of other characters. Further, some pedigrees contain apparently valid instances in which offspring are darker than either parent. A three-factor mechanism of inheritance is proposed: *RST* in Negro and *rst* in White; it is assumed that "the effects of each dose of a gene are cumulative (not dominant) and that the effects of *R* and *S* are such that *S* produces a yellower skin than *R*, while *T* has a smaller effect, so that the genotype involving *TT* is distinguishable from that involving *tt* but not from the

heterozygote." The premise that skin pigment consists of melanin alone (p. 238) is a mistake. The three-factor hypothesis might be strengthened by the recognition of other pigments that exist in skin, melanoid and carotene, so that individual variability would not have been dependent on fluctuations in quantity and distribution of one pigment alone.

The frontispiece is a plate of color squares designed as standards for studies of skin color in Negroes, though it is not clear whether the author and his students used these standards. Of the nine squares, one represents the color of a selected White and eight are reproductions of the colors of as many Negroes, the individuals having been chosen so as to be "spaced as equally as possible within the whole range of skin-color variation." The adequacy of the color samples for matching and their permanence can be determined only by systematic trial and by time; the reviewer has not yet had opportunity to test the colors beyond using them on a few immediately available subjects, where fair matching was obtained.

The collection of pedigrees forms an important contribution of new materials on human inheritance. However, any reader who is acquainted with genetics and physical anthropology will find points in the analysis that he would question. It is not purposed to catalogue such details here or to list irrelevancies and lapses of unity and coherence.

The author is well aware that his families present much racial mixture, for he not only states this explicitly in the Introduction but records the behavior of certain traits in such crosses. It is unfortunate that a biologist makes it appear that he espouses the social classification in a genetic approach to the Negro race, especially when broad generalizations on the mode of inheritance in this "race" as compared with Whites are involved. A brief statement in the Introduction would have sufficed to explain the short-cut usage of the terms "Negro" and "race" and to emphasize that considerations of Negroes as a race are vitiated by the unavoidable dependence on a racially mixed population.

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Principles of Human Genetics

By CURT STERN (Department of Zoölogy, University of California, Berkeley, Calif.). San Francisco: W. H. Freeman Co., 1949. Pp. xi +617, with 198 text figures. $5.50.

THERE is a satisfactory text for human genetics at last! While this announcement is not likely to excite the masses, it is of considerable interest to those who teach a course in human genetics. This book will certainly decrease the professor's problems and improve his mind.

The reviewer would not have agreed to take time to write this article had he not been certain in advance that the book would be an excellent one. Though favorably biased in advance, the praise which follows is thought to be completely honest. It would be surprising if, after reading the book, the reader does not agree that it would be difficult to give too much praise to it. The volume is a masterpiece of writing for the students it is intended for. The last few chapters could well be required reading for all students of the social and natural sciences. It should prove to be highly stimulating to any intelligent person.

Before discussing the contents of the book a few words could be spent on its general appearance. The print gives the impression of being unusually large and it is very easy on the eyes. The drawings by Dr. Aloha Hannah are extremely clever and clear cut. But the reproductions of a few of the more ancient photographs are not very good. No doubt the author will remedy this artistic flaw in the next edition.

Several bright ideas have been utilized in the arrangement of the 27 chapters. One which

impressed the reviewer was that of separating the chapter concerned mainly with mitosis from that on meiosis. The wedge between them is a consideration of genic action. It is a little unusual to consider interactions between genes and substrates, cleavage and differentiation, and the development of syndromes in between mitosis and meiosis. However, the procedure is not alogical and it does provide "reader-interest" early in the book. Students usually find accounts of mitosis and meiosis quite deadly but the treatment here is much more sprightly than what one is accustomed to.

Chapters 5, 6 and 7 concern the fundamentals of probability, single factor inheritance, and lethal genes. The author was able to cover these subjects with distinction in 39 pages, including illustrations, problems and references.

The next chapter comes at an unexpected spot; it probably represents the same tactic employed before of inserting "reader-interest" material where it will prevent an unbroken recital of fundamentals. The subject is that of counseling in human genetics. This occupation is one which the reviewer has embarked upon on a large scale. Consequently the discussion of "Problems of Genetic Advisers," is of especial interest to him. The author uses a pedigree of Lutman and Neel for dominant juvenile cataract very effectively to show how much harm may be avoided and how much worrying may be relieved if consultants in human genetics become widely available to the public. He does not provide any magic formula for the financial support of these future public institutions, but that is, of course, outside the scope of the book.

The philosophy for counseling individuals about dominant deleterious genes is clear to most anyone. That for recessive characters is somewhat less obvious. If a person with a rare deleterious recessive marries, there is little chance of his producing children also showing the defect because the probability that he would marry a carrier is remote. But as a result of his reproduction the undesirable gene may be permitted to continue instead of being eliminated. At some later date the homozygous condition may again be produced, although its occurrence could have been prevented by action at the present time. Such conflicts between the happiness of one generation and the possible unhappiness of an unknown later one are all too common in practical problems of human genetics. The decision, in such cases, is not the task of the scientist, as such, but of the individual or society in general. The reviewer might add to the statement given above by Professor Stern that it would be an inert scientist indeed who failed to form an opinion. Usually the advisee insists upon learning what this opinion is, and is confused and frustrated if it is not given. The individual may not follow the advice but always appears to be grateful for it, whatever it may be. All of the cases involve lack of knowledge and understanding and a clear statement seems to provide great peace of mind.

Once again there are three chapters of fundamentals served up in a most palatable form. Genetic Ratios, the Hardy-Weinberg Law and Multiple Alleles are unusually clearly done. It would seem that the arithmetic, which is so often confusing to students and others, is so straight-forward and well demonstrated that anyone would have to make an effort to fail to comprehend it. A great deal of work went into these chapters and they are models of lucid writing and teaching.

Chapter 12, "the breather", is on medicolegal genetics. Considering the excellence of the other chapters this one is a little disappointing in that it does not point out that other common traits such as eye color and P.T.C. tests could be used in addition to the universally known blood groups. In the past only exclusion of paternity—but not positive assignment of paternity—could be made. Considering the thousands of possible serological combinations in conjunction with the common traits tests available today it would seem to the reviewer that not only may all the wrongly designated men be excluded but in addition it can

be determined whether the genetic father is actually among the candidates tested. There would be much less doubt about this than is usual in legal decisions. In general, medicolegal genetics is not being utilized to the extent to which it has validity.

The acid test of a person's ability to teach the principles of human genetics probably can be found in the treatment of human linkage. This test has been passed with flying colors. The reader will understand the ideas involved and, as he is spared the difficult mathematics involved in actual autosomal recessive calculations, will be ready to stay with the book.

The next two chapters on irregular expression of genes and prenatal interactions are easy reading. At the same time they are definitely relevant and essential to an understanding of the genetics of man.

The treatment of multifactor inheritance is not merely a review of the literature but contains ingenious original applications of the data. The study of the Davenports on skin color has been examined most carefully and the assumption of two main pairs of factors found at least satisfactory for rough work. Consequently it was possible to calculate, on a random mating basis, the eventual equilibrium for skin color in the United States. Assuming an original African component of 10% of the population one would expect an ultimate skin color classification of our population to be 66% white, 26% light mulatto, 5% mulatto, 0.4% dark mulatto and 0.01% black. The author does not expect the reader to revere his decimal points, and realizes that random mating does not occur at present, but the general prediction seems to make sense.

In the chapter on consanguinity the point that a decrease in family size automatically results in a decrease in rate of marriages between relatives is neatly demonstrated. The author points out that the exclusion of consanguinity in a particular generation transfers the load of affected individuals to later generations. He leaves the question open as to whether we should accept our defectives now or postpone them till later. The reviewer prefers postponing the defectives because we may expect medicine to provide palliatives for some of them as time goes on. Perhaps we can do something about the action of individual genes in the future!

The chapter on the sex-ratio is an exceptionally fine statistical job. Apparently there *are* large families which have significant excesses of boys in some cases and girls in others!

This is the place to bring up the only criticism of any magnitude that the reviewer has of the book. It is too long. The author is well aware of this and points it out in his preface. This difficulty is more important at Universities which are on the quarter system than at those with half-year terms. The problem is not an easy one. In assigning the book to his classes it seems impossible for the reviewer to leave out any section—with the possible exception of pages 418–452. These include the chapter on significance of mutations. This chapter is particularly timely because of the increased importance of radiations in our lives. None-the-less it is the only one that the reviewer would consider sacrificing. The failure of the author and reviewer to find a remedy for the excessive length does not remove the difficulty.

In the last five chapters the author comes into his own. These are the topics which are often considered controversial. The relation of heredity to environment is too often used as a vehicle for a display of one's political philosophy. There is no such fault here. Professor Stern uses the twin studies as the basis for his exposition of genetic and environmental contributions to variability. He recognizes the pitfalls of twin studies and does a truly scientific job of placing exactly the right emphasis upon them. It is impossible to convey to the reader an idea of the skill with which the complicated subject matter of these last chapters has been developed. The only way in which one can obtain this insight is to read the book.

The discussion of selection and eugenics has been printed separately in *Science*. Probably most readers have seen it there. They will agree that it should allay the fears of those who expect a collapse of our society due to dysgenic breeding within the next few generations. On the other hand the author does *not* accuse all those interested in Eugenics of being Fascists with castration complexes. He states that even if "the loss of supposedly desirable genotypes in one, or many, generations of differential fertility is small it does not remove the fact that it *is* a loss which may be regrettable and, possibly, even have serious consequences. To state that reproductive selection against severe defects will reduce the number of the affected from one generation to the next by only a few per cent does not alter the fact that these few per cent may mean tens of thousands of unfortunate individuals who, if never born, will be saved untold sorrow. Conversely, even a slight increase of desirable genotypes would be a social gain."

The two chapters devoted to the races of man are not likely to provide support for extremists of any description. The facts of biological similarities and differences are thoughtfully evaluated and a clear distinction drawn between the biological facts themselves and their relation to social race problems.

The last chapter concerns the evolution of man and the primates with a very intriguing discussion of their similarities in polymorphic characters such as the blood groups. A consideration of population genetics is the background for the conclusion that, as the population size of the species Homo sapiens has become very large, it will take longer for decisive changes in gene frequencies to become established or eliminated. Mutation pressure in the future may lead to the further reduction and disappearance of organs or functions which have already ceased to be vital. Population pressures by themselves should prove to be very conservative factors in the evolutionary changes of the future. The author thinks that evolutionary changes, as a result of cultural forces, may be swift and extensive. "The control by man of his own biological evolution will become imperative, since the power which knowledge of human genetics will gradually place in man's hands cannot but lead to action."

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Human Genetics Syllabus

By HERLUF H. STRANDSKOV (Department of Zoölogy, University of Chicago, Chicago 37, Ill.). University of Chicago Press, 1949. Pp. 148.

COURSES in human genetics are increasing in number and playing an increasingly important part in the college curriculum. However, the development of good courses in human genetics has been retarded by lack of suitable textbooks. *Human Genetics Syllabus* is a real contribution to instruction in this field. It consists of directions, problems and discussion topics for an introductory course in human genetics.

The questions and problems are thought-provoking, and many make the student correlate the facts he has learned; some should stimulate reference reading. Real understanding of a subject comes through analysis of problems. The student who wrestles with some of these problems without feeling the need for final answers has learned much.

The pages are printed on one side only, thus providing blank pages for notes. Also there is space after each question or problem for the answer. This feature of the book makes it especially valuable to the student for purposes of review. The book covers a wide range of material for a term's course. The first part of the text is devoted to general genetic prin-

ciples, followed by a consideration of a few statistical concepts, and the last sixty pages deal exclusively with human genetics.

The emphasis on drill in genetic principles will probably meet with general approval, for experience indicates that the average student needs much of this to gain a functional knowledge of the subject.

The author has included a list of textbooks for readings in genetics, an outline of his lecture topics for a quarter, and suggestions for the preparation of a term paper, together with a list of suitable topics on which to write.

Human Genetics Syllabus is new, adaptable, and thorough. It is good, genetically and pedagogically.

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BIBLIOGRAPHY OF HUMAN GENETICS

THIS section, prepared by the Editor, continues the current list of research articles and books of interest to students of human heredity. For information concerning the arrangement of titles, abbreviations for medical serials, and authors' addresses, see Part I of the 1949 list (*Am. J. Human Genet.* 1: 105–112).

[*] indicates that author's address is given in Part 1 of the 1949 list.

1949—PART 2

ANONYMOUS. War and the sex ratio of births. *Statist. Bull. Metrop. Life Insur.* 39(6): 5–7.

ARSLANIAN, J., & MAJDALANI, E. Dystrophie coxo-fémorale héréditaire bilatérale. *Arch. fr. pédiat.* 6(1): 100–104. [Beyrouth, Lebanon]

BARNES, E. W. The mixing of races and social decay. *Eugen. Rev.*, Lond. 41(1): 11–16, Discussion, 28–31.

BEET, E. A. The genetics of the sickle-cell trait in a Bantu tribe. *Ann. Eugen.*, Cambr. 14(4): 279–284. [Colonial Med. Service, Northern Rhodesia]

BENON, R. Hérédité et pathologie mentale; biologie. *Avenir méd.*, Lyon, 46(3): 52.

BERNARD, J., & DEGEORGE, M. Grossesse gémellaire ditopique extra-utérine et intra-utérine; anémie hypochrome du jumeau survivant. *Arch. fr. pédiat.* 6(1): 54–56. [*]

BERNSTEIN, M. E. The middigital hair genes; their inheritance and distribution among the white race. *J. Hered.* 40(5): 127–131. [Arvelighets Institutt, Univ. Oslo, Norw.]

BINNEY, C. Legal and social implications of artificial insemination. *Eugen. Rev.*, Lond. 40(4): 199–204.

BLOOMFIELD, P. The eugenics of the Utopians; the Utopia of the eugenists. *Eugen. Rev.*, Lond. 40(4): 191–198.

BOCK, M., FREIIN VON FINCK, M., & EILERS, M. Ein Fall von Icterus gravis neonatorum infolge Unverträglichkeit des Blutkörperchenmerkmals A_1. *Klin. Wschr.* 27(13–14): 240–241. [Farbenfabriken Bayer, Elberfeld, Germ.]

BÖRNER. Familiäre Nagelatrophie mit Verkümmerung der Augenbrauen und Wimpern. *Derm. Wschr.* 120(8): 267.

BOLTZ, W. Die Verteilung der Blutgruppen und M-N-Faktoren im Untersuchungsmaterial des Institutes in den Jahren 1944 bis 1948. *Wien. klin. Wschr.* 61(15): 234.

BONNET, G. F. Caractère héréditaire de la cholécystatonie. *Arch. mal. app. digest.*, Par. 38(5–6): 378–383. [Vichy, France]

BOORMAN, K. E., DODD, B. E., & TRINICK, R. H. Haemolytic disease of the newborn due to anti-A antibodies. *Lancet*, Lond. 1(26): 1088–91. [South London Blood Supply Depot, Sutton, Surrey, Eng.]

BORCHARDT. Aufgaben und Ziele der Konstitutionsforschung. *Wien. klin. Wschr.* 61(22): 351.

BOWLEY, C. C., & DUNSFORD, I. The agglutinin anti-M associated with pregnancy. *Brit. M. J.* 2(4629): 681–682. [Obstetric Registrar, N. Middlesex Hosp., N. Middlesex, Eng.]

BOYD, W. C. Systematics, evolution, and anthropology in the light of immunology. *Q. Rev. Biol.* 24(2): 102–108. [60 E. Concord St., Boston, Mass.]

BRÉGEAT, P., & NAUD, G. Un nouveau cas de dysostose mandibulofaciale (Syndrome de Franceschetti). *Arch. opht.*, Par. 9(4): 427–440. [Naud: 30 Rue Abbé-Rousselot, Angoulême, France]

BRODNY, M. L., & ROSEN, D. The urologist and artificial insemination. *J. Urol.*, Balt. 61(5): 960–966. [636 Beacon St., Boston, Mass.]

BROOKS, W. D. W., HEASMAN, M. A., & LOVELL, R. R. H. Retinitis pigmentosa associated with cystinuria; two uncommon inherited conditions occurring in a family. *Lancet*, Lond. 1(26): 1096–1098. [148 Harley St., London W. 1, Eng.]

CAMPBELL, J. L., JR. Hereditary hemorrhagic telangiectasia as a cause of hematuria; two case reports. *J. Urol.*, Balt. 62(1): 80–88. [103 W. Brookwood Dr., Valdosta, Ga.]

CHENEY, E. A. Extraction and nonextraction in identical twins. *Am. J. Orthodont.* 35(5): 351–363. [320 W. Ottawa St., Lansing, Mich.]

CHINI, V., & MALAGUZZI VALERI, C. Mediterranean hemopathic syndromes. *Blood*, N. Y. 4(9): 989–1013. [Clinica Medica, Univ. Bari, Italy]

CHOISSER, R. M., & MONTGOMERY, R. R. Gaucher's disease in a Negro; report of case. *Am. J. Clin. Path.* 19(6): 570–575. [1335 H St., N. W., Washington, D. C.]

COFFEY, J. D., JR., SALMON, D. D. Cooley's erythroblastic anemia in a Negro girl. *J. Pediat.*, S. Louis, 34(5): 621–625. [Dept. Pediatrics, Charity Hosp., Shreveport, La.]

CORNBLEET, T., SCHORR, H. C., & BARSKY, S. Pseudo-ophiasis and sickle cell anemia. *Arch. Derm. Syph.*, Chic., 59(5): 519–521. [Dept. Dermatology, Univ. Illinois College of Med., Chicago, Ill.]

CUENDET, J. F., & DELLA PORTA, V. Une famille de nystagmiques. *Ophthalmologica*, Basel, 117(4/5): 199–201. [Clinique Ophtal. Univ., 13 Av. de France, Lausanne, Switz.]

DE ASÚA, F. J. Ovalocitosis en gemelos fraternos. *Rev. Soc. Argent. Hemat.* 1(1): 35. [Libertad 1163, Buenos Aires, Argent.]

DELASCIO, D., CASTRO, A. DE, & CIARI JÚNIOR, C. Gravidez dupla mono-amniótica. *Rev. gin. obst.*, Rio. 43(6): 301–311.

DHOTEL, Y. L'hérédité hypertonique; cancer et hypertension. *Union méd.*, Par. 29(5): 147–154.

DICKINSON, A. Race mixture; a social or a biological problem. *Eugen. Rev.*, Lond. 41(2): 81–85.

DIDION, H. Vergleichend-histopathologische Untersuchungen an einen Zwillingspaar mit Niemann-Pickscher Krankheit. *Frankf. Zschr. Path.* 60(1–2): 194–227. [Wilhelmstrasse 7, Frankenberg-Eder, Germ.]

DITTMER, H. J. A color-blind mother and son. *J. Hered.* 40(5): 126.

DUNSFORD, I. A saline agglutinating Kell antibody. *Nature*, Lond. 163(4155): 962. [*]

DUNSFORD, I. Techniques to overcome the lack of rare Rhesus antisera and cells. *J. Laborat. Clin. M.* 34(8): 1151–1153.

DUYZINGS. Epidermolysis bullosa hereditaria (Koebner) *Ned. tschr. verlosk.* 48(5): 324–328.

ERWIN, W. G., & CORKERN, R. W. A pedigree of partial anodontia. *J. Hered.* 40(8): 215–218. [*Corkern:* Natchitoches, La.]

EYQUEM, A. L'hérédité des groupes sanguins; conceptions actuelles. *Annee biol.* 53(3–4): 49–72.

FADEM, R. S. Ovalocytosis associated with the sickle cell trait. *Blood*, Balt., 4(5): 505–510.

FALLS, H. F. Congenital and hereditary eye diseases. *Sightsav. Rev.* 19(2): 67–78. [*]

FINNEY, D. J. The truncated binomial distribution. *Ann. Eugen.*, Cambr. 14(4): 319–328. [Oxford Univ., Oxford, Eng.]

FRANÇOIS, J. Dystrophie dermo-chondro-cornéene familiale. *Bull. Acad. méd. Belgique* 14(3): 135–171. [Oogheelkundige Kliniek, Rijksuniv., Gent, Belg.]

FRANÇOIS, J. Contribution a l'étude des hérédodégénérescences tapéto-rétiniennes (dégénérescence choriorétinienne familiale à hérédité dominante; coexistence familiale

de la dégénérescence pigmentaire de la rétine et de la maladie de Stargardt.) *Ophthalmologica*, Basel, 118(1): 1–29.

GAFFURI, G. Contributo all'osservazione di gemelli monozigoti. *Scientia genet.* 3(2): 195–201. [Lab. di Biol. Generale, Univ. Cattolica, Milano, Italy]

GARDNER, E. J., & STEPHENS, F. E. Schizophrenia in monozygotic twins. *J. Hered.* 40(6): 165–167. [Lab. Human Genetics, Univ. Utah, Salt Lake City, Utah]

GATES, R. R. *Pedigrees of Negro Families.* Philadelphia: Blakiston Co., pp. 267. [Harvard Univ. Biol. Labs., 16 Divinity Ave., Cambridge 38, Mass.]

GILBERT-DREYFUS, MAMOU, H., & WEISSENBACH, R. Neurofibromatose familiale avec lacunes craniennes multiples. *Bull. Soc. méd. hôp. Paris*, 65(21–22): 806–812.

GIRAUD, P., BOCCA, P., *et al.* Deux familles de dystrophies polyépiphysaires dont une avec synostose cranienne associée. *Arch. fr. pédiat.* 6(1): 110.

GRANADY, J. T. W. An investigation to determine the earliest age of sickle cell anaemia or sickle cell trait in the newborn. *Harlem Hosp. Bull. N. Y.* 1(4): 154–157.

GRUBB, R., & MORGAN, W. T. J. The Lewis blood group characters of erythrocytes and body fluids. *Brit. J. Exp. Path.* 30(3): 198–208. [Inst. of Bacteriology, Univ. Lund, Sweden]

GRUBER, G. B. Zur Kenntnis kranialer Doppelbildung beim Menschen mit Zwerchfellsfehlern und mit Herzbeutel-Lunge. *Beitr. path. Anat.* 110(2): 346–360. [Planckstrasse 8, Göttingen 20, Germ.]

GRUBER, G. B. Zur Kenntnis und Kritik der Osteogenesis imperfecta congenitalis. *Virchows Arch.* 316(3–4): 317–340.

GUASCH, J. Nature familiale et héréditaire de l'elliptocytose humaine. *Acta haemat.*, Basel, 2(3): 178–187. [Instituto Policlinico, Barcelona, Spain]

HALDANE, J. B. S. Parental and fraternal correlations for fitness. *Ann. Eugen.*, Cambr. 14(4): 288–292. [*]

HALDANE, J. B. S. A test for homogeneity of records of familial abnormalities. *Ann. Eugen.*, Cambr. 14(4): 339–341.

HALLGREN, B. Konstitutionell dyslexi (s.k. congenital ordblindhet); klinisk och ärvsbiologisk undersökning. *Nord. med.* 41(1): 14–16. [Ärftlighetspsykiatriska Laboratoriet, Karolinska Sjukhuset, Stockholm 60, Sweden]

HARRIS, H. The incidence of parental consanguinity in diabetes mellitus. *Ann. Eugen.*, Cambr. 14(4): 293–300. [Galton Lab., Univ. College, London, W.C. 1, Eng.]

HARRIS, H., & KALMUS, H. Genetical differences in taste sensitivity to phenylthiourea and to anti-thyroid substances. *Nature*, Lond. 163(4153): 878.

HARRIS, H., & SMITH, C. A. B. The sib-sib age of onset correlation among individuals suffering from a hereditary syndrome produced by more than one gene. *Ann. Eugen.*, Cambr. 14(4): 309–318.

HOCH, M. O. Clover-leaf tongues. *J. Hered.* 40(5): 132. [Dept. Biology, Western Reserve Univ., Cleveland, Ohio]

HOLT, B. A quantitative survey of the finger-prints of a small sample of the British populations. *Ann. Eugen.*, Cambr. 14(4): 329–338. [Galton Lab., Univ. College, London, W.C.1, Eng.]

HOLZER, F. J. Neue Erkenntnisse auf den Gebiete der Blutgruppenforschung. *Wien. klin. Wschr.* 61(9): 129–133.

HUBINONT, O. P. Iso-immunization by blood-group factors A and B in man. *Brit. M. J.* 2(4627): 574–575. [*]

HUIZINGA, J. The digital formula in relation to age, sex and constitutional type. *Proc Kon. Ned. Akad. Wetens.* 52(4): 403–411; 587–593.

IMPERATO, C. L'oligofrenia fenilpiruvica. *Lattante*, 20(4): 238–241.

IRWIN, M. R. Immunological studies in embryology and genetics. *Q. Rev. Biol.* 24(2): 109–123. [Dept. Genetics, Univ. Wisconsin, Madison 6, Wisc.]

JACKSON, M. Familial lumbo-sacral syringomyelia and the significance of developmental errors of the spinal cord and column. *Med. J. Australia*, 1(14): 433–439. [Royal Prince Alfred Hosp., Sydney, Australia]

JOHNSON, S. A. M., & FALLS, H. F. Ehlers-Danlos syndrome; a clinical and genetic study. *Arch. Derm. Syph.*, Chic. 60(1): 82–105. [Dept. Dermatology, Univ. Wisconsin, Madison 6, Wisc.]

KALLMANN, F. J., & SENDER, G. Twin studies on senescence. *Am. J. Psychiat.* 106(1): 29–36. [*]

KAPLAN, R., GRUMBACH, J., *et al.* Grand rachitisme chez un frère jumeau, sans attiente de la soeur jumelle. *Arch. fr. pédiat.* 6(3): 289–290.

KEIZER, D. P. R. Lipodystrophia progressiva (ziekte van Barraquer-Ferré). *Ned. tschr. geneesk.* 93(1): 26–30. [Bergweg 10, Hilversum, Netherl.]

KILBOURNE, E. D. Heredofamilial cerebellar ataxia with spastic paralysis and spinal muscular atrophy; report of two cases of an unusual syndrome. *J. Nerv. Ment. Dis.* 109(5): 409–417. [Dept. Medicine, New York Hosp., N.Y.C.]

KLAUSGRABER, F. Pelger-Huetsche Kernanomalie. *Wien. klin. Wschr.* 61(9): 144.

KLEIN, R. E. The Rh factor and related subjects. *J. Bowman Gray School M.* 7(3): 95–103. [Bowman Gray School of Med., Winston-Salem, N. C.]

KÖRBLER, J. Über gesunde Nachkommenschaft nach Radiumbestrahlung der männlichen Keimdrüsse. *Radiol. clin.*, Basel, 18(4): 240–244. [Zagreb, Yugoslavia]

KRETSCHMER, W. Zur Wechselung der konstitutionell-hereditären und psychisch-reaktiven Gegebenheiten bei der Entstehung von Neurosen. *Zschr. menschl. Vererb.* 29: 62–68. [Universitäts-Nervenklinik, Osianderstrasse 24, Tübingen, Germ.]

LAMY, M., FÈVRE, M., & SÉE, G. Sténose hypertrophique du pylore chez deux jumeaux monozygotiques. *Arch. fr. pédiat.* 6(1): 57–58. [Hôp. des Enfants Malades, 149 Rue de Sevres, Paris, France]

LANG, C. A. An analytical representation of Rh genotypes. *Acta haemat.*, Basel, 2(4): 238–241. [Istituto di Patologia, Ospedali Riuniti, Trieste, Italy]

LAWLER, S. D., & BERTINSHAW, D. A pedigree showing some rare Rh genotypes. *Ann. Eugen.*, Cambr. 14(4): 285. [Lister Inst., London, S.W. 1, Eng.]

LEBRÓN, E. J., & BONATTI, A. A. Grupos sanguíneos y factor Rh en Tucumán. *Rev. Soc. Argent. Hemat.* 1(1): 41–48.

LELONG, M., BORNICHE, *et al.* Mongolien issu de mère mongolienne. *Arch. fr. pédiat.* 6(3): 231–238. [Clinique de Puériculture, Faculté de Méd., 74 Rue Denfert-Rochereau, Paris 14, France]

LENZI, M. Radiazioni ed eredo-patologia. *Rass. clin. sc.* 25(4): 107; passim.

LEONE, C. Profilassi delle mutazioni. *Policlinico, (sez. prat.)* 56(19): 584–586.

LEVINE, P. Isoimmunization by the Rh factor. *Postgrad. M.* 5(6): 451–459. [*]

LEVINE, P., WIGOD, M., *et al.* The Kell-Cellano (K-k) genetic system of human blood factors. *Blood*, Balt. 4(7): 869–872.

LEVRAT, M., BRETTE, R., et al. Les facteurs héréditaires dans l'ulcère gastroduodénal. *Arch. mal. app. digest.*, Par. 38(5–6): 481–486.

LINDSAY, L. Heredity versus practice. *Dent. Rec.*, Lond., 69(2): 31–40.

LISCH, K. Ueber familiäres Vorkommen von spontanem pulsierendem Exophthalmus. *Ophthalmologica*, Basel, 117(3): 180–185. [Wörgl 2, Tyrol, Austria]

LISCHI, G. Foramina parietalia permagna, fenestrae parietales simmetricae; rara malforma-

zione ereditaria del cranio. ***Radiol. med.***, Tor. 35(6): 445–451. [Istituto di Radiologia, Univ. Pisa, Italy)

LUCIA, S. P., HUNT, M. L., & TALBOT, J. C. On the relationship of blood group A to Rh immunization and the occurrence of hemolytic disease of the newborn. *Science*, 110 (2857): 329–330. [Univ. California Med. School, San Francisco, Cal.]

MCLAUGHLIN, C. W., JR. Pseudohemophilia or chronic thrombasthenia *Arch. Surg.* 58(5): 635–645.

MACHADO, L. M. Sobre a incidência da eritroblastose fetal. ***Rev. gin. obst.***, Rio. 43(6): 330–334.

MACUMBER, H. H. Chronic essential pentosuria; a report of three cases. *J. Oklahoma M. Ass.* 42(7): 281. [Chickasha Hosp., Chickasha, Okla.]

MARGERIN. Sur un cas de cataractes congénitales familiales. ***Arch opht.***, Par. 9(2): 209.

MATHEWSON, F. A. L. & LEDERMAN, J. M. Familial non-haemolytic jaundice. *Canad. M. Ass. J.* 60(4): 404. [Winnipeg General Hosp., Winnipeg, Man., Canada]

MAUTNER, H., & QUINN, K. V. Phenylpyruvic oligophrenia. ***Ann. paediat.***, Basel, 172(1): 1-27. [Wrentham State School, Wrentham, Mass.]

MEIER, A. A study of the racial ancestry of the Mississippi college Negro. *Am. J. Phys. Anthrop.* 7(2): 227–239. [Dept. History, Tougaloo College, Tougaloo, Miss.]

MIKULA, F. Familiární výskyt myopathie u tří sourozenců. *Cas. lék. česk.* 88(19): 545.

MILLS, H., & LUCIA, S. P. Familial hypochromic anemia associated with post-splenectomy erythrocyte inclusion bodies. ***Blood***, Balt. 4(8): 891–904. [Univ. California Med. School, San Francisco, Cal.]

MITCHELL, N., MOSS, A. H., ***et al.*** Congenital hemolytic disease resulting from A-O isoimmunization. ***Pediatrics***, Springf. 3(6): 813–819. [Dept. Pathology, Beth-El Hosp., Brooklyn, N. Y.]

MOEHLIG, R. C. Arachnodactyly (Marfan's syndrome); two case reports with etiological implications. *Am. J. Roentg.* 61(6): 797–807. [964 Fisher Bldg., Detroit, Mich.]

MOLLISON, P. L., & CUTBUSH, M. Haemolytic disease of the newborn due to anti-A antibodies. ***Lancet***, Lond. 257(6569): 173. [Blood Transfusion Research Unit, Postgraduate Med. School of London, London, Eng.]

MOURANT, A. E. Rh phenotypes and Fisher's CDE notation. ***Nature***, Lond. 163(4154): 913. [*]

MUSSIO-FOURNIER, J. C., CONTI, O., ***et al.*** Traitement des troubles visuels de l'albinisme par l'hormone mélanophore. ***Bull. Acad. nat. méd.*** 133(21–22): 443–445. [Endocrinologic Inst., Univ. Montevideo, Uruguay]

MUTHER-WIDMER, M. Das Eheverbot des Art. 97ZGB und der Ehe- und Familienschutz. ***Pro infirmis***, Zür. 7(7): 204–209.

NICOLAS, G. Denture et hérédité. *Schweiz. Mschr. Zahnh.* 59(7): 565–575 [Clinique Odontologique, Univ. Genève, Switz.]

NIGAM, R. A case of a xiphopagus monster. ***Ind. J. Surg.*** 11(1): 40–44.

NOBILE, T. Gemellarità e gemelli. ***Ginecologia***, Tor. 15(6): 254–266.

NORTH, N. H., DAWSON, J. B. & TROTTER, W. D. A case of conjoint thoracopagus twins with obstructed labour and delivery by Caesarean section. *J. Obst. Gyn. Brit. Empire*, 56(1): 89–94. [Dept. Obstetrics, Univ. Otago, Otago, New Zealand]

OLIVER-GOMZÁLEZ, J., & GONZÁLEZ, L. M. Release of the A_2 isoagglutinogen-like substance of infectious organisms into human blood serum. *J. Infect. Dis.* 85(1): 66–71. [Western Reserve Univ. School of Med., Cleveland, Ohio]

ORGLER, A. Observations on identical twins. ***Ann. paediat.***, Basel, 172(5–6): 375. [Bromley, Eng.]

OSTERTAG, B. Über ererbte und erworbene Konstitution vom Standpunkt des Pathologen *Zschr. menschl. Vererb.* 29: 157–173. [Hornschuchstrasse 4, Tübingen-Lustnau, Germ.]

OTTENSOOSER, F., & VERSIANI, V. Exclusão alternativa de paternidade por Rh-Hr. *Arq. biol.*, S. Paulo, 33(2): [*]

PATERSON, J. H. Hysteria in one of a pair of identical twins. *J. Neur.*, Lond. 12(2): 160–164. [National Hosp., Queen Square, London, Eng.]

PENROSE, L. S. Garrod's conception of inborn error and its development. *Biochem. J.*, Lond. 44(3): Suppl. p. xvi. [*]

PENROSE, L. S. The meaning of "fitness" in human populations. *Ann. Eugen.*, Cambr. 14(4): 301–304.

PENROSE, L. S. *Biology of Mental Defect.* New York: Grune & Stratton. pp. xi, 285.

PFÄNDLER, U. L'irréversibilité de certaines manifestations héréditaires. *Schweiz. med. Wschr.* 79(16): 363. [La Chaux-de-Fonds, Switz.]

PHILIPOWICZ, J. Ulkuskrankheit bei Zwillingen. *Wien. klin. Wschr.* 61(21): 333.

PICKFORD, R. W. Colour vision of heterozygotes for sex-linked red-green defects. *Nature*, Lond. 163(4151): 804. [*]

PICKFORD, R. W. The genetics of intelligence. *J. Psychol*, Provincet. 28: 129–145.

PLANSON & CHEVELET. A propos d'un cas de sténose pylorique familiale. *Arch. fr. pédiat.* 6(1): 58–60. [Dijon, France]

PLATE, W. P. Een geval van migratio externa van het bevruchtende spermatozoön. *Ned. tschr. verlosk.* 48(5): 298–300.

POPPER, L. Erbe und Umwelt bei der Tuberkulose. *Wien. klin. Wschr.* 61(19): 289–292.

RACE, R. R., SANGER, R., *et al.* The Lewis blood groups of 79 families. *Brit. J. Exp. Path.* 30(1): 73–83. [*]

RACE, R. R., SANGER, R., *et al.* The inheritance of the MNS blood groups: a second series of families. *Heredity*, 3(2): 205–213.

RAMÓN GUERRA, A. U. Trombopatía constitucional hereditaria; seudohemofilia Willebrand-Jürgens. *Arch. Pediat. Uruguay*, 20(3): 151–158.

RAMOS, J. P. La fecundación artificial de los seres humanos. *Dia med.*, B. Air. 21(10): 329–334.

REIMER, E. E. Zum Wesen der Hämophilie. *Wien. klin. Wschr.* 61(21): 335.

REYNOLDS, E. L. Anthropology and human growth. *Ohio J. Sc.* 49(3): 89–91. [Fels Inst., Yellow Springs, Ohio]

RIBEIRO, V. R. L. Estudo estatístico sôbre a incidencia do fator Rh no Distrito Federal. *Vida med.*, Rio. 17(2): 24–26.

RIMINGTON, C. The interpretation of biochemical detail revealed by inborn errors. *Biochem. J.*, Lond. 44(3): Suppl., p. xvii.

ROBERTS, W. R. Hereditary dentinogenesis imperfecta (opalescent dentine). *Brit. Dent. J.* 87(1): 6–10.

ROTH, F. Epignathus parasiticus; ein Beitrag zur Formalgenese des parasitischen Doppelbildungen. *Frankf. Zschr. Path.* 60(1–2): 115–149. [Pathologisches Inst., Univ. Bonn, Germ.]

SACHS, B. Ueber die Genese des angeborenen partiellen Riesenwuchses und ihre Beziehung zur Zwillings- und Geschwulstentstehung. *Arch. Kinderh.* 136(1): 23–34. [Lichtenbergstrasse 19, Darmstadt, Germ.]

SCHACHTER, M. Cataracte congénitale et idiotie, comme embryopathie rougeoleuse. *Praxis*, Bern, 38(19): 421–423. [*]

SCHWARTZ, S. O., & MASON, J. Mediterranean anemia in the Negro; a report of four cases and their families. *Blood*, Balt., 4(6): 706–721. [Cook County Hosp., Chicago 12, Ill.]

SÉDAN, J. Glaucome et relations sexuelles. *Rev. otoneur., Par.* 21(3): 148–155.

SILVA, J. A. Blood groups of the Filipinos. *Acta med. philip.* 5(3): 41–44.

SIMMONS, R. T. The Rh antibody specificities found in 115 human anti-Rh sera. *Med. J. Australia*, 1(20): 633–636. [Commonwealth Serum Labs., Melbourne, Australia]

SMITH, A. U. Some antigenic properties of mammalian spermatozoa. *Proc. R. Soc., Lond.* Ser. B. 136(882): 46–66, 3 pl. [National Institute for Medical Research, Hampstead, London, N.W. 3, Eng.]

SMITH, C. H. Chronic congenital aregenerative anemia (pure red-cell anemia) associated with iso-immunization by the blood. *Blood*, Balt., 4(6): 697–705. [Dept. Pediatrics, Cornell Univ. Med. College, New York, N. Y.]

SIMMONS, R. T., GRAYDON, J. J., & AVIAS, J. Blood-group, M-N type and Rh type frequencies in New Caledonians and the Loyalty and Pine Islanders. *Med. J. Australia*, 1(23): 733–740.

SOYSA, E. Familial periodic paralysis. *Brit. M. J.* 2(4625): 470–471. [British Military Hosp., Colombo, Ceylon]

SPRONG, D. H., JR., & KIRBY, F. G. Familial carotid body tumors; report of nine cases in 11 siblings. *Ann. West. M. & S.* 3(7): 241. [1137 Second St., Santa Monica, Cal.]

STAMPA, U. Zum Entwurf für das Bundesgesetz über Ehe- und Familienschutz bei Geisteskrankheit und Geistesschwäche. *Pro infirmis*, Zür. 7(7): 197–204.

STERN, C. Selection and eugenics. *Science*, 110(2852): 201–212. [Dept. of Zoölogy, Univ. California, Berkeley, Cal.]

STERN, C. *Principles of Human Genetics*. San Francisco: W. H. Freeman & Co. pp. xi + 617.

STRANDSKOV, H. H. *Human Genetics Syllabus (Directions, problems, and discussion topics for an introductory course in human genetics)*. Univ. Chicago Press. pp. 1–164. [*]

STRANDSKOV, H. H. AND BISACCIA, H. The sex ratio of human stillbirths at each month of uterogestation and at conception. *Am. J. Phys. Anthrop.* 7(2): 131–143.

STRATTON, F., & RENTON, P. H. The rhesus factor D^u. *Brit. M. J.* 2(4629): 682–684. [Univ. Manchester, Eng.]

TANISSA, A. Dysplasie ectodermique héréditaire (anidrose, hypotrichose et anodontie) et altérations endocrinienne. *Ann. derm. syph.*, Par. 9(2): 171–175.

THOMPSON, E. A., WALKER, E. T., & WEENS, H. S. Iliac horns; an osseous manifestation of hereditary arthrodysplasia associated with dystrophy of the fingernails. *Radiology*, 53(1): 88–92. [Emory Univ. School of Med., Atlanta 3, Ga.]

TISDALL, L. H., & HARTNETT, E. T., Erythroblastosis fetalis due to blood group A-B-O incompatibility. *N. York State J. M.* 49(14): 1699–1701. [615 Third St., Brooklyn, N. Y.]

WAARDENBURG, P. J. Cliniek en erfelijkheidsleer. *Ned. tschr. tschr. geneesk.* 93(17): 1290–1294. [Velperveg 22, Arnhem, Netherl.]

WEBER, F. P. A fragment of the vast subject of multiple developmental abnormalities. *Med. Press*, Lond. 222(4): 82.

WEDGE, B., & ABE, S. Racial incidence of mental disease in Hawaii. *Hawaii M. J.*, 8(5): 337–338. [9819 Greenwood St., Chicago, Ill.]

WEIMER, B. R. Congenital inheritance of inguinal hernia. *J. Hered.* 40(8): 219–220. [Bethany College, Bethany, W. Va.]

WERGELAND, H. On the cause of familial deaths in early childhood, with particular reference to some uncommon conditions. *Acta paediat.*, Upps. 37(1): 73–86. [Pediatric Dept. State Hosp., Copenhagen, Denm.]

WICINSKI, Z. Przypadek zespolu niebieskich twardówek. (Blue sclera syndrome.) *Polski tygod. lek.* 4(12): 368.

WIENER, A. S. Further observations on isosensitization to the Rh factor. *Proc. Soc. Exp. Biol.*, N. Y. 70(4): 576–578. [*]

WIENER, A. S. Pathogenesis of erythroblastosis fetalis and the Shwartzman phenomenon. *Exp. M. & S.* 7(2–3): 200–212.

WIENER, A. S., & GORDON, E. B. Studies on the blood factor rh^{w}. *Am. J. Clin. Path.* 19(7): 621–629.

WILDERVANCK, L. S. Erfelijke aangeboren afwijkingen van skelet (luxatie van het Capitulum radii; luxatie, hypoplasie of ontbreken van de patella) en nagels. *Ned. tschr. geneesk.* 93(31): 2576–2583. [Hooge der A 10, Groningen, Netherl.]

WILLIAMS, C., & WILLIAMS, C., JR. Intussusception due to familial adenoma of the small intestine. *Arch. Surg.* 59(2): 250–257. [805 W. Franklin St., Richmond 20, Va.]

WILLIAMS, R. J., BERRY, L. J., & BEERSTECHER, E., JR. Individual metabolic patterns, alcoholism, genetotrophic diseases. *Proc. Nat. Acad. Sc. U. S.*, 35(6): 265–271. [*]

WILSON, W. M. G. Congenital blindness (pseudoglioma) occurring as a sex-linked developmental anomaly. *Canad. M. Ass. J.*, 60(6): 580–584. [Dept. of Ophthalmology, Univ. Toronto, Ont., Canada]

WINTER, G. R., & MAIOCCO, P. D. Osteogenesis imperfecta and odontogenesis imperfecta. *Oral Surg.* 2(6): 782–798. [4001 Spruce St., Philadelphia, Pa.]

WOLFSON, W. Q., GUTERMAN, H. S., *et al.* An endocrine finding apparently characteristic of gout. *J. Clin. Endocr.* 9(8): 497–513. [Michael Reese Hosp., Chicago 16, Ill.]

WOLFSON, W. Q., HUNT, H. D., *et al.* The transport and excretion of uric acid in man; a sex difference in urate metabolism; with a note on clinical and laboratory findings in gouty women. *J. Clin. Endocr.* 9(8): 749–767.

WOO, J. Racial and sexual differences in the frontal curvature and its relation to metopism. *Am. J. Phys. Anthrop.* 7(2): 215–226. [Dept. Anatomy, Washington Univ. School of Med., St. Louis, Mo.]

WOODSIDE, M. Sterilization and social welfare; a survey of current developments in North Carolina. *Eugen. Rev.*, Lond., 40(4): 205–210.

WURZBACH, F. A., JR., & BUNKIN, I. A. Unilateral acute hydramnios in uniovulvar twin pregnancy. *J. Obst. Gyn. Brit. Empire*, 56(2): 242–245. [Morrisania City Hosp., New York, N. Y.]

YI, C. L., CHOW, Y. C., & LIU, Y. M. The distribution of the Rh factor among Chinese. *Sc. & Techn. China*, 2(1): 10. [Dept. Physiology, National Hsian-Ya Med. College, Changsha, China]

ZIEGLER, E. Kasuistische Beiträge aus dem Gebiet des Morbus haemolyticus neonatorum. *Ann. paediat.*, Basel, 172(4): 226–230. [Winterthur, Switz.]

ZSCHUNKE. Habituelle Aphthen, familiär bei unregelmässig dominantem Erbgang mit Bevorzugung der männlichen Sippenangehörigen. *Derm. Wschr.* 120(8): 266.

Notice to Subscribers and Librarians

This number of the *Journal* completes Volume One, and the ensuing number (March, 1950) now in preparation will be designated as Volume Two, Number One. This change in the publication plan was adopted by the Society's Board of Directors in order that a regular March, June, September, December schedule of publication might be established as soon as possible, thus avoiding an overlapping of volumes and years. Individual and institutional subscribers will be credited with half of their 1949 subscription ($4.00) towards their subscription to Volume Two (1950). A similar adjustment has been made in the 1950 dues for active and corresponding members. Further information will be sent to members and subscribers through the office of the Secretary, Dr. H. H. Strandskov, Department of Zoology, University of Chicago, Chicago 37, Illinois.

A *Title Page, Table of Contents,* and *Index* will be compiled for the first two volumes combined and will be included with the December issue of Volume Two. Those who wish to bind their copies of the *Journal* will therefore find it expedient to combine the six issues of Volumes One and Two.

Errata

American Journal of Human Genetics, Volume 1, Number 1

p. 60, line 17 from *bottom:* insert square bracket at end of line.
p. 61, line 5 from *top:* insert $\frac{1}{2}$ at beginning of the expression.
p. 61, line 2 from *bottom:* delete the first minus sign.
p. 64, line 2 from *top:* second term in square brackets should be $3sxy^2$.
p. 82, line 12 from *top:* for 'All of the unusual anaphases and telophases . . .' read 'All of the unusual spermatocytes . . .'